

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 01 May 2001 (01.05.01)	
International application No. PCT/US00/16636	Applicant's or agent's file reference PF-0733 PCT
International filing date (day/month/year) 16 June 2000 (16.06.00)	Priority date (day/month/year) 16 June 1999 (16.06.99)
Applicant YUE, Henry et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 09 January 2001 (09.01.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Olivia TEFY Telephone No.: (41-22) 338.83.38
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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PF-0733 PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 16636	International filing date (day/month/year) 16/06/2000	(Earliest) Priority Date (day/month/year) 16/06/1999
Applicant INCYTE GENOMICS, INC et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☐

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒

contained in the international application in written form.

☐

filed together with the international application in computer readable form.

☐

furnished subsequently to this Authority in written form.

☒

furnished subsequently to this Authority in computer readable form.

☒

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐

the text is approved as submitted by the applicant.

☒

the text has been established by this Authority to read as follows:

HUMAN INTRACELLULAR SIGNALING MOLECULES

5. With regard to the **abstract**,

☒

the text is approved as submitted by the applicant.

☐

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐

as suggested by the applicant.

☐

because the applicant failed to suggest a figure.

☐

because this figure better characterizes the invention.

☐

None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IS 00/16636

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C07K14/47 C07K16/18 C12Q1/68 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K C12Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 15587 A (DUKE UNIVERSITY) 1 May 1997 (1997-05-01)	1,3, 6-16,18, 19,22, 25-27 2,4,5,17
A	abstract page 6, line 17 -page 7, line 5 page 16, line 4 -page 32, line 15 page 48 -page 56; examples 5-8 page 66 -page 69; claims 1-25 page 70 -page 72; figures 1A,1B,2 --- -/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

12 October 2000

Date of mailing of the international search report

11. 1. 01

Name and mailing address of the ISA

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Fuchs, U

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/16636

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EMBL database, Heidelberg, FRG Emest Hum3 accession number AI083494 18 August 1998 NCI-CGAP: "ox75a07.x1 Soares NhHMPu S1 Homo sapiens cDNA clone IMAGE:1662132 3' similar to TR:Q13802 Q13802 ARGBPIB PROTEIN, mRNA sequence" XP002149761 the whole document	11-15
A	--- WO 97 44347 A (SMITHKLINE BEECHAM CORP., PRESIDENT AND FELLOWS HARVARD COLLEGE) 27 November 1997 (1997-11-27) abstract page 5, line 21 - line 28 page 29, line 21 -page 32, line 28 page 43 -page 46; claims 1-28 ---	1-19,22, 25-27
A	--- US 5 602 019 A (BEAVO, J.A. ET AL.) 11 February 1997 (1997-02-11) abstract column 7, line 31 - line 67 column 21, line 1 -column 27, line 2 column 127 -column 128; claims 1-7,10-25 -----	1-19,22, 25-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC 00/16636

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9715587	A	01-05-1997	US 5969101 A	19-10-1999
			AU 7520396 A	15-05-1997

WO 9744347	A	27-11-1997	AU 5926296 A	09-12-1997

US 5602019	A	11-02-1997	US 5389527 A	14-02-1995
			US 6015677 A	18-01-2000
			US 5580771 A	03-12-1996
			US 5800987 A	01-09-1998
			US 5789553 A	04-08-1998
			US 5776752 A	07-07-1998
			CA 2085881 A	20-10-1992
			EP 0535216 A	07-04-1993
			WO 9218541 A	29-10-1992

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 20, 21, 23 and 24

Claims 20, 21, 23 and 24 refer to an agonist and an antagonist of a polypeptide of claim 1 without giving a true technical characterization. Moreover, no such compounds are defined in the application. In consequence, the scope of said claims is ambiguous and vague, and their subject matter is not sufficiently disclosed and supported (Art. 5 and 6 PCT).

No search can be carried out for such purely speculative claims whose wording is, in fact, a mere recitation of the result to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/16636

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 20, 21, 23 and 24
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-19, 22, 25-27 partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-19, 22, 25-27 partially

Invention 1

An isolated polypeptide comprising an amino acid sequence selected from the group consisting of: a) an amino acid sequence having the SEQ ID NO: 1, b) a naturally occurring amino acid sequence having at least 90% sequence identity to SEQ ID NO: 1, c) a biologically active fragment of SEQ ID NO: 1, d) an immunogenic fragment of SEQ ID NO: 1; an isolated polynucleotide encoding said polypeptide; a recombinant polynucleotide comprising said polynucleotide; a cell transformed with said recombinant polynucleotide; a transgenic organism comprising said recombinant polynucleotide; a method for producing said polypeptide; an isolated antibody which specifically binds to said polypeptide; an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of: a) a polynucleotide sequence having the SEQ ID NO: 53, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to SEQ ID NO: 53, c) a polynucleotide sequence complementary to a); d) a polynucleotide sequence complementary to b); an RNA equivalent of a)-d); a method for detecting a target polynucleotide in a sample having the sequence of said polynucleotide by hybridizing with a probe or by PCR; a pharmaceutical composition comprising an effective amount of said polypeptide; a method for treating a disease or condition associated with decreased expression of functional OXRD, comprising administering to a patient said pharmaceutical composition; a method for screening a compound for effectiveness as an agonist or antagonist of said polypeptide; a method for screening for a compound that specifically binds to said polypeptide or that modulates the activity of said polypeptide; a method for screening a compound for effectiveness in altering expression of a polynucleotide sequence having the SEQ ID NO: 53;

2. Claims: 1-19, 22, 25-27 partially

Invention 2

Idem as subject 1 but limited to SEQ ID NOS: 2 and 54;

3.-50. Claims: 1-19, 22, 25-27 partially

Inventions 3-50

Idem as subject 1 but limited to SEQ ID NOS: 3-31, 34-52 and 55-83, 86-104.

(19) World Intellectual Property Organization
International Bureau



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21 December 2000 (21.12.2000)

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60/164,417 9 November 1999 (09.11.1999) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier applications:

US 60/149,640 (CIP)
Filed on 17 August 1999 (17.08.1999)
US 60/164,417 (CIP)
Filed on 9 November 1999 (09.11.1999)
US 60/139,566 (CIP)
Filed on 16 June 1999 (16.06.1999)

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(74) Agents: HAMLET-COX, Diana et al.; Incyte Genomics, Inc., 3160 Porter Drive, Palo Alto, CA 94304 (US).

(81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— Without international search report and to be republished upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INTRACELLULAR SIGNALING MOLECULES

(57) Abstract: The invention provides human intracellular signaling molecules (INTRA) and polynucleotides which identify and encode INTRA. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of INTRA.

WO 00/77040 A2

INTRACELLULAR SIGNALING MOLECULES

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of intracellular signaling molecules and to the use of these sequences in the diagnosis, treatment, and prevention of cell proliferative, autoimmune/inflammatory, neurological, gastrointestinal, reproductive, and developmental disorders.

BACKGROUND OF THE INVENTION

Cell-cell communication is essential for the growth, development, and survival of multicellular organisms. Cells communicate by sending and receiving molecular signals. An example of a molecular signal is a growth factor, which binds and activates a specific transmembrane receptor on the surface of a target cell. The activated receptor transduces the signal intracellularly, thus initiating a cascade of biochemical reactions that ultimately affect gene transcription and cell cycle progression in the target cell.

Intracellular signaling is the process by which cells respond to extracellular signals (hormones, neurotransmitters, growth and differentiation factors, etc.) through a cascade of biochemical reactions that begins with the binding of a signaling molecule to a cell membrane receptor and ends with the activation of an intracellular target molecule. Intermediate steps in the process involve the activation of various cytoplasmic proteins by phosphorylation via protein kinases, and their deactivation by protein phosphatases, and the eventual translocation of some of these activated proteins to the cell nucleus where the transcription of specific genes is triggered. The intracellular signaling process regulates all types of cell functions including cell proliferation, cell differentiation, and gene transcription, and involves a diversity of molecules including protein kinases and phosphatases, and second messenger molecules such as cyclic nucleotides, calcium-calmodulin, inositol, and various mitogens that regulate protein phosphorylation.

Intracellular signaling is carried out by a variety of molecules that promote the transduction and amplification of the signal. For example, binding of a ligand to a transmembrane receptor activates membrane-associated intracellular proteins, such as G-proteins. G-proteins mediate both the level of intracellular second messengers, such as cyclic AMP, and the activity of signaling enzymes, such as phospholipase C. These messengers and enzymes then activate signal transduction pathways, many of which are mediated by protein kinase cascades. Phosphorylation of proteins in response to extracellular signals, cell cycle checkpoints, and environmental or nutritional stresses is often accomplished by transfer of a high energy phosphate from ATP. Second messengers whose effects are mediated by protein kinases include cyclic AMP, cyclic GMP, inositol triphosphate, cyclic ADP

ribose, and calcium/calmodulin. Alternatively, binding of ligand to a transmembrane receptor, such as a receptor tyrosine kinase, triggers the activation of a molecular "switch," such as a monomeric GTPase. In this case, binding of ligand to the receptor activates a catalytic domain in the intracellular portion of the receptor. This activated domain then switches on the activity of monomeric GTPases such as Ras, usually via adaptor proteins.

Cells also respond to changing conditions by switching off signals. Many signal transduction proteins are short-lived and rapidly targeted for degradation by covalent ligation to ubiquitin, a highly conserved small protein. Cells also maintain mechanisms to monitor changes in the concentration of denatured or unfolded proteins in membrane-bound extracytoplasmic compartments, including a transmembrane receptor that monitors the concentration of available chaperone molecules in the endoplasmic reticulum and transmits a signal to the cytosol to activate the transcription of nuclear genes encoding chaperones in the endoplasmic reticulum.

Certain proteins in intracellular signaling pathways serve to link or cluster other proteins involved in the signaling cascade. These proteins are referred to as scaffold, anchoring, or adaptor proteins. (For review, see Pawson, T., and Scott, J.D. (1997) Science 278:2075-2080.) As many intracellular signaling proteins such as protein kinases and phosphatases have relatively broad substrate specificities, the adaptors help to organize the component signaling proteins into specific biochemical pathways.

Gangliosides, generally associated with plasma membranes, also participate in signal transduction. Aberrant ganglioside function has been implicated in inflammatory and degenerative diseases within and outside of the nervous system, including Tay-Sachs disease, multiple sclerosis, lupus erythematosus, and insulin-dependent diabetes mellitus (Misasi, R. et al. (1997) Diabetes Metab. Rev. 13:163-179).

Many of the above signaling molecules are characterized by the presence of particular domains that promote protein-protein interactions. A sampling of these domains is discussed below, along with other important intracellular messengers.

Intracellular Signaling Second Messenger Molecules

Phospholipid and Inositol-phosphate Signaling

Inositol phospholipids (phosphoinositides) are involved in an intracellular signaling pathway that begins with binding of a signaling molecule to a G-protein linked receptor in the plasma membrane. This leads to the phosphorylation of phosphatidylinositol (PI) residues on the inner side of the plasma membrane to the biphosphate state (PIP₂) by inositol kinases. Simultaneously, the G-protein linked receptor binding stimulates a trimeric G-protein which in turn activates a phosphoinositide-specific phospholipase C-β. Phospholipase C-β then cleaves PIP₂ into two

products, inositol triphosphate (IP_3) and diacylglycerol. These two products act as mediators for separate signaling events. IP_3 diffuses through the plasma membrane to induce calcium release from the endoplasmic reticulum (ER), while diacylglycerol remains in the membrane and helps activate protein kinase C, an STK that phosphorylates selected proteins in the target cell. The calcium response initiated by IP_3 is terminated by the dephosphorylation of IP_3 by specific inositol phosphatases. Cellular responses that are mediated by this pathway are glycogen breakdown in the liver in response to vasopressin, smooth muscle contraction in response to acetylcholine, and thrombin-induced platelet aggregation.

Cyclic Nucleotide Signaling

Cyclic nucleotides (cAMP and cGMP) function as intracellular second messengers to transduce a variety of extracellular signals including hormones, light, and neurotransmitters. In particular, cyclic-AMP dependent protein kinases (PKA) are thought to account for all of the effects of cAMP in most mammalian cells, including various hormone-induced cellular responses. Visual excitation and the phototransmission of light signals in the eye is controlled by cyclic-GMP regulated, Ca^{2+} -specific channels. Because of the importance of cellular levels of cyclic nucleotides in mediating these various responses, regulating the synthesis and breakdown of cyclic nucleotides is an important matter. Thus adenylyl cyclase, which synthesizes cAMP from AMP, is activated to increase cAMP levels in muscle by binding of adrenaline to β -adrenergic receptors, while activation of guanylate cyclase and increased cGMP levels in photoreceptors leads to reopening of the Ca^{2+} -specific channels and recovery of the dark state in the eye. In contrast, hydrolysis of cyclic nucleotides by cAMP and cGMP-specific phosphodiesterases (PDEs) produces the opposite of these and other effects mediated by increased cyclic nucleotide levels. PDEs appear to be particularly important in the regulation of cyclic nucleotides, considering the diversity found in this family of proteins. At least seven families of mammalian PDEs (PDE1-7) have been identified based on substrate specificity and affinity, sensitivity to cofactors, and sensitivity to inhibitory drugs (Beavo, J.A. (1995) *Physiological Reviews* 75:725-48). PDE inhibitors have been found to be particularly useful in treating various clinical disorders. Rolipram, a specific inhibitor of PDE4, has been used in the treatment of depression, and similar inhibitors are undergoing evaluation as anti-inflammatory agents. Theophylline is a nonspecific PDE inhibitor used in the treatment of bronchial asthma and other respiratory diseases (Banner, K.H. and Page, C.P. (1995) *Eur. Respir. J.* 8:996-1000).

Calcium Signaling Molecules

Ca^{+2} is another second messenger molecule that is even more widely used as an intracellular mediator than cAMP. Two pathways exist by which Ca^{+2} can enter the cytosol in response to extracellular signals: One pathway acts primarily in nerve signal transduction where Ca^{+2} enters a nerve terminal through a voltage-gated Ca^{+2} channel. The second is a more ubiquitous pathway in

which Ca^{2+} is released from the ER into the cytosol in response to binding of an extracellular signaling molecule to a receptor. Ca^{2+} directly activates regulatory enzymes, such as protein kinase C, which trigger signal transduction pathways. Ca^{2+} also binds to specific Ca^{2+} -binding proteins (CBPs) such as calmodulin (CaM) which then activate multiple target proteins in the cell including enzymes, membrane transport pumps, and ion channels. CaM interactions are involved in a multitude of cellular processes including, but not limited to, gene regulation, DNA synthesis, cell cycle progression, mitosis, cytokinesis, cytoskeletal organization, muscle contraction, signal transduction, ion homeostasis, exocytosis, and metabolic regulation (Celio, M.R. et al. (1996) Guidebook to Calcium-binding Proteins, Oxford University Press, Oxford, UK, pp. 15-20). Some Ca^{2+} binding proteins are characterized by the presence of one or more EF-hand Ca^{2+} binding motifs, which are comprised of 12 amino acids flanked by α -helices (Celio, supra). The regulation of CBPs has implications for the control of a variety of disorders. Calcineurin, a CaM-regulated protein phosphatase, is a target for inhibition by the immunosuppressive agents cyclosporin and FK506. This indicates the importance of calcineurin and CaM in the immune response and immune disorders (Schwaninger M. et al. (1993) J. Biol Chem. 268:23111-23115). The level of CaM is increased several-fold in tumors and tumor-derived cell lines for various types of cancer (Rasmussen, C.D. and Means, A.R. (1989) Trends in Neuroscience 12:433-438).

The annexins are a family of calcium-binding proteins that associate with the cell membrane (Towle, C.A. and Treadwell, B.V. (1992) J. Biol. Chem. 267:5416-23). Annexins reversibly bind to negatively charged phospholipids (phosphatidylcholine and phosphatidylserine) in a calcium dependent manner. Annexins participate in various processes pertaining to signal transduction at the plasma membrane, including membrane-cytoskeleton interactions, phospholipase inhibition, anticoagulation, and membrane fusion. Annexins contain four to eight repeated segments of about 60 residues. Each repeat folds into five alpha helices wound into a right-handed superhelix.

25 **Signaling Complex Protein Domains**

PDZ domains were named for three proteins in which this domain was initially discovered. These proteins include PSD-95 (postsynaptic density 95), Dlg (Drosophila lethal(1)discs large-1), and ZO-1 (zonula occludens-1). These proteins play important roles in neuronal synaptic transmission, tumor suppression, and cell junction formation, respectively. Since the discovery of these proteins, over sixty additional PDZ-containing proteins have been identified in diverse prokaryotic and eukaryotic organisms. This domain has been implicated in receptor and ion channel clustering and in the targeting of multiprotein signaling complexes to specialized functional regions of the cytosolic face of the plasma membrane. (For review of PDZ domain-containing proteins, see Ponting, C. P. et al. (1997) Bioessays 19:469-479.) A large proportion of PDZ domains are found in the eukaryotic MAGUK (membrane-associated guanylate kinase) protein family, members of which bind to the

intracellular domains of receptors and channels. However, PDZ domains are also found in diverse membrane-localized proteins such as protein tyrosine phosphatases, serine/threonine kinases, G-protein cofactors, and synapse-associated proteins such as syntrophins and neuronal nitric oxide synthase (nNOS). Generally, about one to three PDZ domains are found in a given protein, although
5 up to nine PDZ domains have been identified in a single protein. The glutamate receptor interacting protein (GRIP) contains seven PDZ domains. GRIP is an adaptor that links certain glutamate receptors to other proteins and may be responsible for the clustering of these receptors at excitatory synapses in the brain (Dong, H. et al. (1997) *Nature* 386:279-284).

The SH3 domain is defined by homology to a region of the proto-oncogene c-Src, a
10 cytoplasmic protein tyrosine kinase. SH3 is a small domain of 50 to 60 amino acids that interacts with proline-rich ligands. SH3 domains are found in a variety of eukaryotic proteins involved in signal transduction, cell polarization, and membrane-cytoskeleton interactions. In some cases, SH3 domain-containing proteins interact directly with receptor tyrosine kinases. For example, the SLAP-130 protein is a substrate of the T-cell receptor (TCR) stimulated protein kinase. SLAP-130 interacts
15 via its SH3 domain with the protein SLP-76 to affect the TCR-induced expression of interleukin-2 (Musci, M.A. et al. (1997) *J. Biol. Chem.* 272:11674-11677). Another recently identified SH3 domain protein is macrophage actin-associated tyrosine-phosphorylated protein (MAYP) which is phosphorylated during the response of macrophages to colony stimulating factor-1 (CSF-1) and is likely to play a role in regulating the CSF-1-induced reorganization of the actin cytoskeleton (Yeung,
20 Y.-G. et al. (1998) *J. Biol. Chem.* 273:30638-30642). The structure of SH3 is characterized by two antiparallel beta sheets packed against each other at right angles. This packing forms a hydrophobic pocket lined with residues that are highly conserved between different SH3 domains. This pocket makes critical hydrophobic contacts with proline residues in the ligand (Feng, S. et al. (1994) *Science* 266: 1241-47). Endophilin is an SH3 domain-containing protein implicated in synaptic vesicle
25 endocytosis. (Micheva, K.D. (1997) 272:27239-27245).

A novel domain, called the WW domain, resembles the SH3 domain in its ability to bind proline-rich ligands. This domain was originally discovered in dystrophin, a cytoskeletal protein with direct involvement in Duchenne muscular dystrophy (Bork, P. and Sudol, M. (1994) *Trends Biochem. Sci.* 19:531-533). WW domains have since been discovered in a variety of intracellular signaling
30 molecules involved in development, cell differentiation, and cell proliferation. The structure of the WW domain is composed of beta strands grouped around four conserved aromatic residues, generally tryptophan.

Like SH3, the SH2 domain is defined by homology to a region of c-Src. SH2 domains interact directly with phospho-tyrosine residues, thus providing an immediate mechanism for the
35 regulation and transduction of receptor tyrosine kinase-mediated signaling pathways. For example, as

many as ten distinct SH2 domains are capable of binding to phosphorylated tyrosine residues in the activated PDGF receptor, thereby providing a highly coordinated and finely tuned response to ligand-mediated receptor activation. (Reviewed in Schaffhausen, B. (1995) *Biochem. Biophys. Acta.* 1242:61-75.)

5 Homer is a neuronal immediate early gene that is enriched at excitatory synapses (Xiao, B. et al. (1998) *Neuron* 21:707-716). Homer proteins form multivalent complexes that bind proline-rich motifs in group I metabotropic glutamate receptors and inositol triphosphate receptors, thereby coupling these receptors in a signaling complex (Tu, J.C. (1999) *Neuron* 23:583-592).

 The pleckstrin homology (PH) domain was originally identified in pleckstrin, the
10 predominant substrate for protein kinase C in platelets. Since its discovery, this domain has been identified in over 90 proteins involved in intracellular signaling or cytoskeletal organization. Proteins containing the pleckstrin homology domain include a variety of kinases, phospholipase-C isoforms, guanine nucleotide release factors, and GTPase activating proteins. For example, members of the FGD1 family contain both Rho-guanine nucleotide exchange factor (GEF) and PH domains, as well
15 as a FYVE zinc finger domain. FGD1 is the gene responsible for faciogenital dysplasia, an inherited skeletal dysplasia (Pasteris, N.G. and Gorski, J.L. (1999) *Genomics* 60:57-66). Many PH domain proteins function in association with the plasma membrane, and this association appears to be mediated by the PH domain itself. PH domains share a common structure composed of two
20 antiparallel beta sheets flanked by an amphipathic alpha helix. Variable loops connecting the component beta strands generally occur within a positively charged environment and may function as ligand binding sites (Lemmon, M. A. et al. (1996) *Cell* 85:621-624.). n-Chimaerin is a GAP involved in the formation of lamellipodia and filopodia in neuroblastoma cells. (Kozma, R. et al. (1996) *Mol. Cell Biol.* 16:5069-5080.)

 Ankyrin (ANK) repeats mediate protein-protein interactions associated with diverse
25 intracellular signaling functions. For example, ANK repeats are found in proteins involved in cell proliferation such as kinases, kinase inhibitors, tumor suppressors, and cell cycle control proteins. (See, for example, Kalus, W. et al. (1997) *FEBS Lett.* 401:127-132; Ferrante, A. W. et al. (1995) *Proc. Natl. Acad. Sci. USA* 92:1911-1915.) These proteins generally contain multiple ANK repeats, each composed of about 33 amino acids. Myotrophin is an ANK repeat protein that plays a key role
30 in the development of cardiac hypertrophy, a contributing factor to many heart diseases. Structural studies show that the myotrophin ANK repeats, like other ANK repeats, each form a helix-turn-helix core preceded by a protruding "tip." These tips are of variable sequence and may play a role in protein-protein interactions. The helix-turn-helix region of the ANK repeats stack on top of one another and are stabilized by hydrophobic interactions (Yang, Y. et al. (1998) *Structure* 6:619-626).

35 The tetratrico peptide repeat (TPR) is a 34 amino acid repeated motif found in organisms

from bacteria to humans. TPRs are predicted to form amphipathic helices, and appear to mediate protein-protein interactions. TPR domains are found in CDC16, CDC23, and CDC27, members the the anaphase promoting complex which targets proteins for degradation at the onset of anaphase. Other processes involving TPR proteins include cell cycle control, transcription repression, stress response, and protein kinase inhibition. (Lamb, J.R. et al. (1995) Trends Biochem. Sci. 20:257-259.)

The armadillo/beta-catenin repeat is a 42 amino acid motif which forms a superhelix of alpha helices when tandemly repeated. The structure of the armadillo repeat region from beta-catenin revealed a shallow groove of positive charge on one face of the superhelix, which is a potential binding surface. The armadillo repeats of beta-catenin, plakoglobin, and p120^{cas} bind the cytoplasmic domains of cadherins. Beta-catenin/cadherin complexes are targets of regulatory signals that govern cell adhesion and mobility. (Huber, A.H. et al. (1997) Cell 90:871-882.)

The discovery of new intracellular signaling proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of cell proliferative, autoimmune/inflammatory, reproductive, and developmental disorders.

SUMMARY OF THE INVENTION

The invention features purified polypeptides, intracellular signaling molecules, referred to collectively as "INTRA" and individually as "INTRA-1," "INTRA-2," "INTRA-3," "INTRA-4," "INTRA-5," "INTRA-6," "INTRA-7," "INTRA-8," "INTRA-9," "INTRA-10," "INTRA-11," "INTRA-12," "INTRA-13," "INTRA-14," "INTRA-15," "INTRA-16," "INTRA-17," "INTRA-18," "INTRA-19," "INTRA-20," "INTRA-21," "INTRA-22," "INTRA-23," "INTRA-24," "INTRA-25," "INTRA-26," "INTRA-27," "INTRA-28," "INTRA-29," "INTRA-30," "INTRA-31," "INTRA-32," "INTRA-33," "INTRA-34," "INTRA-35," "INTRA-36," "INTRA-37," "INTRA-38," "INTRA-39," "INTRA-40," "INTRA-41," "INTRA-42," "INTRA-43," "INTRA-44," "INTRA-45," "INTRA-46," "INTRA-47," "INTRA-48," "INTRA-49," "INTRA-50," "INTRA-51," and "INTRA-52." In one aspect, the invention provides an isolated polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. In one alternative, the invention provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-52.

The invention further provides an isolated polynucleotide encoding a polypeptide comprising

an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. In one alternative, the polynucleotide encodes a polypeptide selected from the group consisting of SEQ ID NO:1-52. In another alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:53-104.

Additionally, the invention provides a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. In one alternative, the invention provides a cell transformed with the recombinant polynucleotide. In another alternative, the invention provides a transgenic organism comprising the recombinant polynucleotide.

The invention also provides a method for producing a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the polypeptide, and b) recovering the polypeptide so expressed.

Additionally, the invention provides an isolated antibody which specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52.

The invention further provides an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). In one alternative, the polynucleotide comprises at least 60 contiguous nucleotides.

Additionally, the invention provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and b) detecting the presence or absence of said hybridization complex, and optionally, if present, the amount thereof. In one alternative, the probe comprises at least 60 contiguous nucleotides.

The invention further provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

The invention further provides a pharmaceutical composition comprising an effective amount of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence

selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and a pharmaceutically acceptable excipient. In one embodiment, the pharmaceutical composition comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The invention additionally
5 provides a method of treating a disease or condition associated with decreased expression of functional INTRA, comprising administering to a patient in need of such treatment the pharmaceutical composition.

The invention also provides a method for screening a compound for effectiveness as an agonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a)
10 an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The
15 method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the invention provides a pharmaceutical composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with decreased expression of functional INTRA, comprising administering to a
20 patient in need of such treatment the pharmaceutical composition.

Additionally, the invention provides a method for screening a compound for effectiveness as an antagonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence
25 selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a pharmaceutical
30 composition comprising an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional INTRA, comprising administering to a patient in need of such treatment the pharmaceutical composition.

The invention further provides a method of screening for a compound that specifically binds
35 to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an

amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The method comprises a) combining the polypeptide with at least one test compound under suitable conditions, and b) detecting binding of the polypeptide to the test compound, thereby identifying a compound that specifically binds to the polypeptide.

The invention further provides a method of screening for a compound that modulates the activity of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-52. The method comprises a) combining the polypeptide with at least one test compound under conditions permissive for the activity of the polypeptide, b) assessing the activity of the polypeptide in the presence of the test compound, and c) comparing the activity of the polypeptide in the presence of the test compound with the activity of the polypeptide in the absence of the test compound, wherein a change in the activity of the polypeptide in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence selected from the group consisting of SEQ ID NO:53-104, the method comprising a) exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

BRIEF DESCRIPTION OF THE TABLES

Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID NOs), clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding INTRA.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms, and searchable databases used for analysis of INTRA.

Table 3 shows selected fragments of each nucleic acid sequence; the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis; diseases,

disorders, or conditions associated with these tissues; and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding INTRA were isolated.

5 Table 5 shows the tools, programs, and algorithms used to analyze the polynucleotides and polypeptides of the invention, along with applicable descriptions, references, and threshold parameters.

DESCRIPTION OF THE INVENTION

10 Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

15 It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

20 Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing
25 the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

"INTRA" refers to the amino acid sequences of substantially purified INTRA obtained from
30 any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which intensifies or mimics the biological activity of INTRA. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of INTRA either by directly interacting with
35 INTRA or by acting on components of the biological pathway in which INTRA participates.

An "allelic variant" is an alternative form of the gene encoding INTRA. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to
5 allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding INTRA include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as INTRA or a
10 polypeptide with at least one functional characteristic of INTRA. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding INTRA, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding INTRA. The encoded protein may also be "altered," and may contain deletions, insertions, or
15 substitutions of amino acid residues which produce a silent change and result in a functionally equivalent INTRA. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of INTRA is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged
20 amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide,
25 polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to a sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence.
30 Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of INTRA. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of INTRA either by
35 directly interacting with INTRA or by acting on components of the biological pathway in which

INTRA participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')₂, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind INTRA polypeptides can be prepared using intact polypeptides or using
5 fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize
10 the animal.

The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures
15 on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition capable of base-pairing with the "sense" (coding) strand of a specific nucleic acid sequence. Antisense compositions may include DNA; RNA; peptide nucleic acid (PNA); oligonucleotides having modified backbone linkages such as
20 phosphorothioates, methylphosphonates, or benzylphosphonates; oligonucleotides having modified sugar groups such as 2'-methoxyethyl sugars or 2'-methoxyethoxy sugars; or oligonucleotides having modified bases such as 5-methyl cytosine, 2'-deoxyuracil, or 7-deaza-2'-deoxyguanosine. Antisense molecules may be produced by any method including chemical synthesis or transcription. Once introduced into a cell, the complementary antisense molecule base-pairs with a naturally occurring
25 nucleic acid sequence produced by the cell to form duplexes which block either transcription or translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand of a reference DNA molecule.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" or "immunogenic"
30 refers to the capability of the natural, recombinant, or synthetic INTRA, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

"Complementary" describes the relationship between two single-stranded nucleic acid sequences that anneal by base-pairing. For example, 5'-AGT-3' pairs with its complement,
35 3'-TCA-5'.

A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding INTRA or fragments of INTRA may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been subjected to repeated DNA sequence analysis to resolve uncalled bases, extended using the XL-PCR kit (PE Biosystems, Foster City CA) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from one or more overlapping cDNA, EST, or genomic DNA fragments using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI) or Phrap (University of Washington, Seattle WA). Some sequences have been both extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that are predicted to least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

	Original Residue	Conservative Substitution
	Ala	Gly, Ser
	Arg	His, Lys
	Asn	Asp, Gln, His
25	Asp	Asn, Glu
	Cys	Ala, Ser
	Gln	Asn, Glu, His
	Glu	Asp, Gln, His
	Gly	Ala
30	His	Asn, Arg, Gln, Glu
	Ile	Leu, Val
	Leu	Ile, Val
	Lys	Arg, Gln, Glu
	Met	Leu, Ile
35	Phe	His, Met, Leu, Trp, Tyr
	Ser	Cys, Thr
	Thr	Ser, Val
	Trp	Phe, Tyr
	Tyr	His, Phe, Trp
40	Val	Ile, Leu, Thr

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide

backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

5 A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to a chemically modified polynucleotide or polypeptide. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule.
10 A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "detectable label" refers to a reporter molecule or enzyme that is capable of generating a measurable signal and is covalently or noncovalently joined to a polynucleotide or polypeptide.

15 A "fragment" is a unique portion of INTRA or the polynucleotide encoding INTRA which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10,
20 15, 16, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50% of a polypeptide) as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the
25 specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:53-104 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:53-104, for example, as distinct from any other sequence in the genome from which the fragment was obtained. A fragment of SEQ ID NO:53-104 is useful, for
30 example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:53-104 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:53-104 and the region of SEQ ID NO:53-104 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-52 is encoded by a fragment of SEQ ID NO:53-104. A
35 fragment of SEQ ID NO:1-52 comprises a region of unique amino acid sequence that specifically

identifies SEQ ID NO:1-52. For example, a fragment of SEQ ID NO:1-52 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-52. The precise length of a fragment of SEQ ID NO:1-52 and the region of SEQ ID NO:1-52 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A "full-length" polynucleotide sequence is one containing at least a translation initiation codon (e.g., methionine) followed by an open reading frame and a translation termination codon. A "full-length" polynucleotide sequence encodes a "full-length" polypeptide sequence.

"Homology" refers to sequence similarity or, interchangeably, sequence identity, between two or more polynucleotide sequences or two or more polypeptide sequences.

The terms "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequences.

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at <http://www.ncbi.nlm.nih.gov/BLAST/>. The BLAST software suite includes various sequence analysis programs including "blastn." that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at <http://www.ncbi.nlm.nih.gov/gorf/bl2.html>. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to

compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Reward for match: 1

5 *Penalty for mismatch: -2*

Open Gap: 5 and Extension Gap: 2 penalties

Gap x drop-off: 50

Expect: 10

Word Size: 11

10 *Filter: on*

Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous
15 nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes
20 in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some
25 alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the charge and hydrophobicity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e
30 sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

35 Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise

comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.12 (Apr-21-2000) with blastp set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

5 *Open Gap: 11 and Extension Gap: 1 penalties*

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10 Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment
15 length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for chromosome replication, segregation and maintenance.

20 The term "humanized antibody" refers to an antibody molecule in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to the process by which a polynucleotide strand anneals with a complementary strand through base pairing under defined hybridization conditions. Specific
25 hybridization is an indication that two nucleic acid sequences share a high degree of complementarity. Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive
30 conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 µg/ml sheared, denatured salmon sperm DNA.

35 Generally, stringency of hybridization is expressed, in part, with reference to the temperature

under which the wash step is carried out. Such wash temperatures are typically selected to be about 5°C to 20°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating T_m and conditions for nucleic acid hybridization are well known and can be found in Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, sheared and denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

An "immunogenic fragment" is a polypeptide or oligopeptide fragment of INTRA which is capable of eliciting an immune response when introduced into a living organism, for example, a mammal. The term "immunogenic fragment" also includes any polypeptide or oligopeptide fragment of INTRA which is useful in any of the antibody production methods disclosed herein or known in the art.

The term "microarray" refers to an arrangement of a plurality of polynucleotides, polypeptides, or other chemical compounds on a substrate.

The terms "element" and "array element" refer to a polynucleotide, polypeptide, or other chemical compound having a unique and defined position on a microarray.

5 The term "modulate" refers to a change in the activity of INTRA. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of INTRA.

10 The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with a second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding
15 sequence. Operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition.
20 PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Post-translational modification" of an INTRA may involve lipidation, glycosylation, phosphorylation, acetylation, racemization, proteolytic cleavage, and other modifications known in the art. These processes may occur synthetically or biochemically. Biochemical modifications will
25 vary by cell type depending on the enzymatic milieu of INTRA.

"Probe" refers to nucleic acid sequences encoding INTRA, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes.
30 "Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

Probes and primers as used in the present invention typically comprise at least 15 contiguous
35 nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also

be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

5 Methods for preparing and using probes and primers are described in the references, for example Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel, F.M. et al., 1987, Current Protocols in Molecular Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis, M. et al., 1990, PCR Protocols. A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs
10 can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

 Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to
15 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from
20 megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection
25 programs may also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both
30 unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

35 A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence

that is made by an artificial combination of two or more otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have
5 been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a
10 vaccinia virus, that could be used to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

A "regulatory element" refers to a nucleic acid sequence usually derived from untranslated regions of a gene and includes enhancers, promoters, introns, and 5' and 3' untranslated regions (UTRs). Regulatory elements interact with host or viral proteins which control transcription,
15 translation, or RNA stability.

"Reporter molecules" are chemical or biochemical moieties used for labeling a nucleic acid, amino acid, or antibody. Reporter molecules include radionuclides; enzymes; fluorescent, chemiluminescent, or chromogenic agents; substrates; cofactors; inhibitors; magnetic particles; and other moieties known in the art.

20 An "RNA equivalent," in reference to a DNA sequence, is composed of the same linear sequence of nucleotides as the reference DNA sequence with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic
25 acids encoding INTRA, or fragments thereof, or INTRA itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or
30 synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide comprising the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

35 The term "substantially purified" refers to nucleic acid or amino acid sequences that are

removed from their natural environment and are isolated or separated, and are at least 60% free, preferably at least 75% free, and most preferably at least 90% free from other components with which they are naturally associated.

5 A "substitution" refers to the replacement of one or more amino acid residues or nucleotides by different amino acid residues or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

10 A "transcript image" refers to the collective pattern of gene expression by a particular cell type or tissue under given conditions at a given time.

"Transformation" describes a process by which exogenous DNA is introduced into a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, bacteriophage or viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

20 A "transgenic organism," as used herein, is any organism, including but not limited to animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or in vitro fertilization, but rather is directed to the introduction of a recombinant DNA molecule. The transgenic organisms contemplated in accordance with the present invention include bacteria, cyanobacteria, fungi, plants, and animals. The isolated DNA of the present invention can be introduced into the host by methods known in the art, for example infection, transfection, transformation or transconjugation. Techniques for transferring the DNA of the present invention into such organisms are widely known and provided in references such as Sambrook et al. (1989), supra.

35 A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of

the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternative splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

THE INVENTION

The invention is based on the discovery of new human intracellular signaling molecules (INTRA), the polynucleotides encoding INTRA, and the use of these compositions for the diagnosis, treatment, or prevention of cell proliferative, autoimmune/inflammatory, neurological, gastrointestinal, reproductive, and developmental disorders.

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding INTRA. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each INTRA were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. In some cases, GenBank sequence identifiers are also shown in column 5. The Incyte clones and GenBank cDNA sequences, where indicated, in column 5 were used to assemble the consensus nucleotide sequence of each INTRA and are useful as fragments in

hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows homologous sequences as identified by BLAST analysis along with relevant citations, all of which are expressly incorporated by reference herein in their entirety; and column 7 shows analytical methods and in some cases, searchable databases to which the analytical methods were applied. The methods of column 7 were used to characterize each polypeptide through sequence homology and protein motifs.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding INTRA. The first column of Table 3 lists the nucleotide SEQ ID NOs. Column 2 lists fragments of the nucleotide sequences of column 1. These fragments are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:53-104 and to distinguish between SEQ ID NO:53-104 and related polynucleotide sequences. The polypeptides encoded by these fragments are useful, for example, as immunogenic peptides. Column 3 lists tissue categories which express INTRA as a fraction of total tissues expressing INTRA. Column 4 lists diseases, disorders, or conditions associated with those tissues expressing INTRA as a fraction of total tissues expressing INTRA. Column 5 lists the vectors used to subclone each cDNA library. Of particular interest is the expression of SEQ ID NO:88 and SEQ ID NO:94 in reproductive tissues, of SEQ ID NO:99, SEQ ID NO:100, and SEQ ID NO:103 in hematopoietic/immune tissues, and of SEQ ID NO:96 in cardiovascular tissues.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding INTRA were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

SEQ ID NO:58 maps to chromosome 7 within the interval from 84.40 to 90.30 centiMorgans. This interval also contains an EST with high similarity to thyroid disease hypothetical autoantigen. SEQ ID NO:67 maps to chromosome 16 within the interval from 119.20 centiMorgans to q-terminus. This interval also contains the paraplegin gene, mutations in which cause spastic paraplegia and OXPHOS impairment. SEQ ID NO:70 maps to chromosome 11 within the interval from 59.50 to 62.50 centiMorgans. SEQ ID NO:71 maps to chromosome 7 within the interval from 138.0 to 145.8 centiMorgans. SEQ ID NO:73 maps to chromosome 12 within the interval from 76.5 to 84.2 centiMorgans. SEQ ID NO:77 maps to chromosome 7 within the interval from 4.8 to 10.6 centiMorgans and to chromosome 4 within the interval from 56.7 to 60.5 centiMorgans. The interval

on chromosome 7 from from 4.8 to 10.6 centiMorgans also contains a gene associated with cell proliferation. The interval on chromosome 4 from 56.7 to 60.5 centiMorgans also contains a gene associated with cell proliferation. SEQ ID NO:79 maps to chromosome 15 within the interval from 32.2 to 47.1 centiMorgans. This interval also contains a gene associated with cell proliferation. SEQ ID NO:80 maps to chromosome 20 within the interval from 50.2 to 53.6 centiMorgans. This interval also contains a gene associated with cell differentiation. SEQ ID NO:84 maps to chromosome 3 within the interval from 142.2 to 148.7 centiMorgans. SEQ ID NO:87 maps to chromosome 5 within the interval from 141.4 to 147.1 centiMorgans. SEQ ID NO:91 maps to chromosome 12 within the interval from 62.7 to 67.3 centiMorgans. SEQ ID NO:95 maps to chromosome 15 within the interval from 45.5 to 58.8 centiMorgans. SEQ ID NO:97 maps to the X chromosome within the interval from 112.8 to 139.4 centiMorgans.

The invention also encompasses INTRA variants. A preferred INTRA variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the INTRA amino acid sequence, and which contains at least one functional or structural characteristic of INTRA.

The invention also encompasses polynucleotides which encode INTRA. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:53-104, which encodes INTRA. The polynucleotide sequences of SEQ ID NO:53-104, as presented in the Sequence Listing, embrace the equivalent RNA sequences, wherein occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The invention also encompasses a variant of a polynucleotide sequence encoding INTRA. In particular, such a variant polynucleotide sequence will have at least about 80%, or alternatively at least about 90%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding INTRA. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:53-104 which has at least about 80%, or alternatively at least about 90%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:53-104. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of INTRA.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding INTRA, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These

combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring INTRA, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode INTRA and its variants are generally capable
5 of hybridizing to the nucleotide sequence of the naturally occurring INTRA under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding INTRA or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with
10 which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding INTRA and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode INTRA and
15 INTRA derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding INTRA or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of
20 hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:53-104 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) *Methods Enzymol.* 152:399-407; Kimmel, A.R. (1987) *Methods Enzymol.* 152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

25 Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (PE Biosystems, Foster City CA), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found
30 in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (PE Biosystems). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (PE Biosystems), the MEGABACE 1000 DNA sequencing
35 system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting

sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

- 5 The nucleic acid sequences encoding INTRA may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.)
- 10 Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom,
- 15 M. et al. (1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-3060). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries
- 20 (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of
- 25 about 68°C to 72°C.

- When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence
- 30 into 5' non-transcribed regulatory regions.

- Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the
- 35 emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate

software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, PE Biosystems), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

5 In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode INTRA may be cloned in recombinant DNA molecules that direct expression of INTRA, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express INTRA.

10 The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter INTRA-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-
15 mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

The nucleotides of the present invention may be subjected to DNA shuffling techniques such as MOLECULARBREEDING (Maxygen Inc., Santa Clara CA; described in U.S. Patent Number 5,837,458; Chang, C.-C. et al. (1999) Nat. Biotechnol. 17:793-797; Christians, F.C. et al. (1999) Nat.
20 Biotechnol. 17:259-264; and Cramer, A. et al. (1996) Nat. Biotechnol. 14:315-319) to alter or improve the biological properties of INTRA, such as its biological or enzymatic activity or its ability to bind to other molecules or compounds. DNA shuffling is a process by which a library of gene variants is produced using PCR-mediated recombination of gene fragments. The library is then subjected to selection or screening procedures that identify those gene variants with the desired
25 properties. These preferred variants may then be pooled and further subjected to recursive rounds of DNA shuffling and selection/screening. Thus, genetic diversity is created through "artificial" breeding and rapid molecular evolution. For example, fragments of a single gene containing random point mutations may be recombined, screened, and then reshuffled until the desired properties are optimized. Alternatively, fragments of a given gene may be recombined with fragments of
30 homologous genes in the same gene family, either from the same or different species, thereby maximizing the genetic diversity of multiple naturally occurring genes in a directed and controllable manner.

In another embodiment, sequences encoding INTRA may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucleic Acids
35 Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Nucleic Acids Symp. Ser. 7:225-232.)

Alternatively, INTRA itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solution-phase or solid-phase techniques. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY, pp. 55-60; and Roberge, J.Y. et al. (1995) *Science* 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (PE Biosystems). Additionally, the amino acid sequence of INTRA, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide or a polypeptide having a sequence of a naturally occurring polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) *Methods Enzymol.* 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, supra, pp. 28-53.)

In order to express a biologically active INTRA, the nucleotide sequences encoding INTRA or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding INTRA. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding INTRA. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding INTRA and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding INTRA and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding INTRA. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus);

5 plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. (See, e.g., Sambrook, supra; Ausubel, supra; Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509; Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544; Scorer, C.A. et al. (1994) Bio/Technology 12:181-184; Engelhard, E.K. et al. (1994) Proc. Natl.

10 Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945; Takamatsu, N. (1987) EMBO J. 6:307-311; Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105; The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196; Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659; and Harrington,

15 J.J. et al. (1997) Nat. Genet. 15:345-355.) Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. (See, e.g., Di Nicola, M. et al. (1998) Cancer Gen. Ther. 5(6):350-356; Yu, M. et al., (1993) Proc. Natl. Acad. Sci. USA 90(13):6340-6344; Buller, R.M. et al. (1985) Nature 317(6040):813-815; McGregor, D.P. et al.

20 (1994) Mol. Immunol. 31(3):219-226; and Verma, I.M. and N. Somia (1997) Nature 389:239-242.) The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding INTRA. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding INTRA can be achieved using a

25 multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORT1 plasmid (Life Technologies). Ligation of sequences encoding INTRA into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of

30 nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of INTRA are needed, e.g. for the production of antibodies, vectors which direct high level expression of INTRA may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of INTRA. A number of vectors

35 containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH

promoters, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra; Bitter, supra; and Scorer, supra.)

5 Plant systems may also be used for expression of INTRA. Transcription of sequences encoding INTRA may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, supra; Broglie, supra; and Winter, supra.) These
10 constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding INTRA may be ligated into
15 an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses INTRA in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-
20 based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet.
25 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of INTRA in cell lines is preferred. For example, sequences encoding INTRA can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector.
30 Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk⁻* and *apr⁻* cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), β glucuronidase and its substrate β -glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding INTRA is inserted within a marker gene sequence, transformed cells containing sequences encoding INTRA can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding INTRA under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding INTRA and that express INTRA may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of INTRA using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on INTRA is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and

Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled
5 hybridization or PCR probes for detecting sequences related to polynucleotides encoding INTRA include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding INTRA, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase
10 such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

15 Host cells transformed with nucleotide sequences encoding INTRA may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode INTRA may be designed to contain signal sequences which
20 direct secretion of INTRA through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or
25 "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

30 In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding INTRA may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric INTRA protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of INTRA activity. Heterologous protein
35 and peptide moieties may also facilitate purification of fusion proteins using commercially available

affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the INTRA encoding sequence and the heterologous protein sequence, so that INTRA may be cleaved away from the heterologous moiety following purification.

10 Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled INTRA may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, ³⁵S-methionine.

15

INTRA of the present invention or fragments thereof may be used to screen for compounds that specifically bind to INTRA. At least one and up to a plurality of test compounds may be screened for specific binding to INTRA. Examples of test compounds include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

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In one embodiment, the compound thus identified is closely related to the natural ligand of INTRA, e.g., a ligand or fragment thereof, a natural substrate, a structural or functional mimetic, or a natural binding partner. (See, Coligan, J.E. et al. (1991) Current Protocols in Immunology 1(2): Chapter 5.) Similarly, the compound can be closely related to the natural receptor to which INTRA binds, or to at least a fragment of the receptor, e.g., the ligand binding site. In either case, the compound can be rationally designed using known techniques. In one embodiment, screening for these compounds involves producing appropriate cells which express INTRA, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or E. coli. Cells expressing INTRA or cell membrane fractions which contain INTRA are then contacted with a test compound and binding, stimulation, or inhibition of activity of either INTRA or the compound is analyzed.

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An assay may simply test binding of a test compound to the polypeptide, wherein binding is detected by a fluorophore, radioisotope, enzyme conjugate, or other detectable label. For example, the assay may comprise the steps of combining at least one test compound with INTRA, either in

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solution or affixed to a solid support, and detecting the binding of INTRA to the compound.

Alternatively, the assay may detect or measure binding of a test compound in the presence of a labeled competitor. Additionally, the assay may be carried out using cell-free preparations, chemical libraries, or natural product mixtures, and the test compound(s) may be free in solution or affixed to a solid support.

INTRA of the present invention or fragments thereof may be used to screen for compounds that modulate the activity of INTRA. Such compounds may include agonists, antagonists, or partial or inverse agonists. In one embodiment, an assay is performed under conditions permissive for INTRA activity, wherein INTRA is combined with at least one test compound, and the activity of INTRA in the presence of a test compound is compared with the activity of INTRA in the absence of the test compound. A change in the activity of INTRA in the presence of the test compound is indicative of a compound that modulates the activity of INTRA. Alternatively, a test compound is combined with an *in vitro* or cell-free system comprising INTRA under conditions suitable for INTRA activity, and the assay is performed. In either of these assays, a test compound which modulates the activity of INTRA may do so indirectly and need not come in direct contact with the test compound. At least one and up to a plurality of test compounds may be screened.

In another embodiment, polynucleotides encoding INTRA or their mammalian homologs may be "knocked out" in an animal model system using homologous recombination in embryonic stem (ES) cells. Such techniques are well known in the art and are useful for the generation of animal models of human disease. (See, e.g., U.S. Patent No. 5,175,383 and U.S. Patent No. 5,767,337.) For example, mouse ES cells, such as the mouse 129/SvJ cell line, are derived from the early mouse embryo and grown in culture. The ES cells are transformed with a vector containing the gene of interest disrupted by a marker gene, e.g., the neomycin phosphotransferase gene (neo; Capecchi, M.R. (1989) Science 244:1288-1292). The vector integrates into the corresponding region of the host genome by homologous recombination. Alternatively, homologous recombination takes place using the Cre-loxP system to knockout a gene of interest in a tissue- or developmental stage-specific manner (Marth, J.D. (1996) Clin. Invest. 97:1999-2002; Wagner, K.U. et al. (1997) Nucleic Acids Res. 25:4323-4330). Transformed ES cells are identified and microinjected into mouse cell blastocysts such as those from the C57BL/6 mouse strain. The blastocysts are surgically transferred to pseudopregnant dams, and the resulting chimeric progeny are genotyped and bred to produce heterozygous or homozygous strains. Transgenic animals thus generated may be tested with potential therapeutic or toxic agents.

Polynucleotides encoding INTRA may also be manipulated *in vitro* in ES cells derived from human blastocysts. Human ES cells have the potential to differentiate into at least eight separate cell lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate

into, for example, neural cells, hematopoietic lineages, and cardiomyocytes (Thomson, J.A. et al. (1998) Science 282:1145-1147).

Polynucleotides encoding INTRA can also be used to create "knockin" humanized animals (pigs) or transgenic animals (mice or rats) to model human disease. With knockin technology, a
5 region of a polynucleotide encoding INTRA is injected into animal ES cells, and the injected sequence integrates into the animal cell genome. Transformed cells are injected into blastulae, and the blastulae are implanted as described above. Transgenic progeny or inbred lines are studied and treated with potential pharmaceutical agents to obtain information on treatment of a human disease. Alternatively, a mammal inbred to overexpress INTRA, e.g., by secreting INTRA in its milk, may
10 also serve as a convenient source of that protein (Janne, J. et al. (1998) Biotechnol. Annu. Rev. 4:55-74).

THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of INTRA and intracellular signaling molecules. In addition, the expression of
15 INTRA is closely associated with cancers of the hematopoietic/immune, nervous, gastrointestinal, and reproductive, systems therefore, INTRA appears to play a role in cell proliferative, autoimmune/inflammatory, neurological, gastrointestinal, reproductive, and developmental disorders. In the treatment of disorders associated with increased INTRA expression or activity, it is desirable to decrease the expression or activity of INTRA. In the treatment of disorders associated with decreased
20 INTRA expression or activity, it is desirable to increase the expression or activity of INTRA.

Therefore, in one embodiment, INTRA or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of INTRA. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed
25 connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, hematopoietic cancer including lymphoma, leukemia, and myeloma; and other cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, adenoma, carcinoma and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia,
30 gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an autoimmune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-
35 candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's

disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma ; and a gastrointestinal disorder such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis, hyperbilirubinemia, cirrhosis, passive congestion of the liver, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, acquired immunodeficiency syndrome (AIDS) enteropathy, jaundice, hepatic encephalopathy, hepatorenal syndrome, hepatic steatosis, hemochromatosis, Wilson's disease, alpha₁-antitrypsin deficiency, Reye's syndrome, primary sclerosing cholangitis, liver infarction, portal vein obstruction and thrombosis, centrilobular necrosis, peliosis hepatis, hepatic vein thrombosis, veno-occlusive disease, preeclampsia, eclampsia, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and a hepatic tumor including a nodular hyperplasia, a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system

disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, akathisia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; and a gastrointestinal disorder such as

5 esophagitis, esophageal carcinoma, gastritis, gastric carcinoma, inflammatory bowel disease, cholecystitis, infections of the intestinal tract, pancreatitis, pancreatic carcinoma, cirrhosis, hepatitis, hepatoma, colitis, colonic carcinoma, and Crohn's disease.

In another embodiment, a vector capable of expressing INTRA or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased

10 expression or activity of INTRA including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified INTRA in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of INTRA including, but not limited to, those provided above.

15 In still another embodiment, an agonist which modulates the activity of INTRA may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of INTRA including, but not limited to, those listed above.

In a further embodiment, an antagonist of INTRA may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of INTRA. Examples of such

20 disorders include, but are not limited to, those cell proliferative, autoimmune/inflammatory, neurological, gastrointestinal, reproductive, and developmental disorders described above. In one aspect, an antibody which specifically binds INTRA may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express INTRA.

25 In an additional embodiment, a vector expressing the complement of the polynucleotide encoding INTRA may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of INTRA including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate

30 therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of INTRA may be produced using methods which are generally known in the art. In particular, purified INTRA may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind INTRA. Antibodies to INTRA may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with INTRA or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to INTRA have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein. Short stretches of INTRA amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to INTRA may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce INTRA-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

5 Antibody fragments which contain specific binding sites for INTRA may also be generated. For example, such fragments include, but are not limited to, $F(ab')_2$ fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. 10 et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between INTRA and its 15 specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering INTRA epitopes is generally used, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for INTRA. Affinity is expressed as an 20 association constant, K_a , which is defined as the molar concentration of INTRA-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple INTRA epitopes, represents the average affinity, or avidity, of the antibodies for INTRA. The K_a determined for a preparation of monoclonal antibodies, which are monospecific 25 for a particular INTRA epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the INTRA-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of INTRA, 30 preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington DC; Liddell, J.E. and A. Cryer (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For 35 example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml,

preferably 5-10 mg specific antibody/ml, is generally employed in procedures requiring precipitation of INTRA-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al., supra.)

5 In another embodiment of the invention, the polynucleotides encoding INTRA, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, modifications of gene expression can be achieved by designing complementary sequences or antisense molecules (DNA, RNA, PNA, or modified oligonucleotides) to the coding or regulatory regions of the gene encoding INTRA. Such technology is well known in the art, and antisense oligonucleotides or larger
10 fragments can be designed from various locations along the coding or control regions of sequences encoding INTRA. (See, e.g., Agrawal, S., ed. (1996) Antisense Therapeutics, Humana Press Inc., Totawa NJ.)

In therapeutic use, any gene delivery system suitable for introduction of the antisense sequences into appropriate target cells can be used. Antisense sequences can be delivered
15 intracellularly in the form of an expression plasmid which, upon transcription, produces a sequence complementary to at least a portion of the cellular sequence encoding the target protein. (See, e.g., Slater, J.E. et al. (1998) *J. Allergy Clin. Immunol.* 102(3):469-475; and Scanlon, K.J. et al. (1995) 9(13):1288-1296.) Antisense sequences can also be introduced intracellularly through the use of viral vectors, such as retrovirus and adeno-associated virus vectors. (See, e.g., Miller, A.D. (1990) *Blood*
20 76:271; Ausubel, supra; Uckert, W. and W. Walther (1994) *Pharmacol. Ther.* 63(3):323-347.) Other gene delivery mechanisms include liposome-derived systems, artificial viral envelopes, and other systems known in the art. (See, e.g., Rossi, J.J. (1995) *Br. Med. Bull.* 51(1):217-225; Boado, R.J. et al. (1998) *J. Pharm. Sci.* 87(11):1308-1315; and Morris, M.C. et al. (1997) *Nucleic Acids Res.* 25(14):2730-2736.)

25 In another embodiment of the invention, polynucleotides encoding INTRA may be used for somatic or germline gene therapy. Gene therapy may be performed to (i) correct a genetic deficiency (e.g., in the cases of severe combined immunodeficiency (SCID)-X1 disease characterized by X-linked inheritance (Cavazzana-Calvo, M. et al. (2000) *Science* 288:669-672), severe combined immunodeficiency syndrome associated with an inherited adenosine deaminase (ADA) deficiency
30 (Blaese, R.M. et al. (1995) *Science* 270:475-480; Bordignon, C. et al. (1995) *Science* 270:470-475), cystic fibrosis (Zabner, J. et al. (1993) *Cell* 75:207-216; Crystal, R.G. et al. (1995) *Hum. Gene Therapy* 6:643-666; Crystal, R.G. et al. (1995) *Hum. Gene Therapy* 6:667-703), thalassemias, familial hypercholesterolemia, and hemophilia resulting from Factor VIII or Factor IX deficiencies (Crystal, R.G. (1995) *Science* 270:404-410; Verma, I.M. and Somia, N. (1997) *Nature* 389:239-242)), (ii)
35 express a conditionally lethal gene product (e.g., in the case of cancers which result from unregulated

cell proliferation), or (iii) express a protein which affords protection against intracellular parasites (e.g., against human retroviruses, such as human immunodeficiency virus (HIV) (Baltimore, D. (1988) *Nature* 335:395-396; Poeschla, E. et al. (1996) *Proc. Natl. Acad. Sci. USA.* 93:11395-11399), hepatitis B or C virus (HBV, HCV); fungal parasites, such as Candida albicans and Paracoccidioides brasiliensis; and protozoan parasites such as Plasmodium falciparum and Trypanosoma cruzi). In the case where a genetic deficiency in INTRA expression or regulation causes disease, the expression of INTRA from an appropriate population of transduced cells may alleviate the clinical manifestations caused by the genetic deficiency.

In a further embodiment of the invention, diseases or disorders caused by deficiencies in INTRA are treated by constructing mammalian expression vectors encoding INTRA and introducing these vectors by mechanical means into INTRA-deficient cells. Mechanical transfer technologies for use with cells in vivo or ex vitro include (i) direct DNA microinjection into individual cells, (ii) ballistic gold particle delivery, (iii) liposome-mediated transfection, (iv) receptor-mediated gene transfer, and (v) the use of DNA transposons (Morgan, R.A. and W.F. Anderson (1993) *Annu. Rev. Biochem.* 62:191-217; Ivics, Z. (1997) *Cell* 91:501-510; Boulay, J-L. and H. Récipon (1998) *Curr. Opin. Biotechnol.* 9:445-450).

Expression vectors that may be effective for the expression of INTRA include, but are not limited to, the PCDNA 3.1, EPITAG, PRCCMV2, PREP, PVAX vectors (Invitrogen, Carlsbad CA), PCMV-SCRIPT, PCMV-TAG, PEGSH/PERV (Stratagene, La Jolla CA), and PTET-OFF, PTET-ON, PTRE2, PTRE2-LUC, PTK-HYG (Clontech, Palo Alto CA). INTRA may be expressed using (i) a constitutively active promoter, (e.g., from cytomegalovirus (CMV), Rous sarcoma virus (RSV), SV40 virus, thymidine kinase (TK), or β -actin genes), (ii) an inducible promoter (e.g., the tetracycline-regulated promoter (Gossen, M. and H. Bujard (1992) *Proc. Natl. Acad. Sci. U.S.A.* 89:5547-5551; Gossen, M. et al. (1995) *Science* 268:1766-1769; Rossi, F.M.V. and H.M. Blau (1998) *Curr. Opin. Biotechnol.* 9:451-456), commercially available in the T-REX plasmid (Invitrogen)); the ecdysone-inducible promoter (available in the plasmids PVGRXR and PIND; Invitrogen); the FK506/rapamycin inducible promoter; or the RU486/mifepristone inducible promoter (Rossi, F.M.V. and H.M. Blau, supra), or (iii) a tissue-specific promoter or the native promoter of the endogenous gene encoding INTRA from a normal individual.

Commercially available liposome transformation kits (e.g., the PERFECT LIPID TRANSFECTION KIT, available from Invitrogen) allow one with ordinary skill in the art to deliver polynucleotides to target cells in culture and require minimal effort to optimize experimental parameters. In the alternative, transformation is performed using the calcium phosphate method (Graham, F.L. and A.J. Eb (1973) *Virology* 52:456-467), or by electroporation (Neumann, E. et al.

(1982) EMBO J. 1:841-845). The introduction of DNA to primary cells requires modification of these standardized mammalian transfection protocols.

In another embodiment of the invention, diseases or disorders caused by genetic defects with respect to INTRA expression are treated by constructing a retrovirus vector consisting of (i) the polynucleotide encoding INTRA under the control of an independent promoter or the retrovirus long terminal repeat (LTR) promoter, (ii) appropriate RNA packaging signals, and (iii) a Rev-responsive element (RRE) along with additional retrovirus *cis*-acting RNA sequences and coding sequences required for efficient vector propagation. Retrovirus vectors (e.g., PFB and PFBNEO) are commercially available (Stratagene) and are based on published data (Riviere, I. et al. (1995) Proc. Natl. Acad. Sci. U.S.A. 92:6733-6737), incorporated by reference herein. The vector is propagated in an appropriate vector producing cell line (VPCL) that expresses an envelope gene with a tropism for receptors on the target cells or a promiscuous envelope protein such as VSVg (Armentano, D. et al. (1987) J. Virol. 61:1647-1650; Bender, M.A. et al. (1987) J. Virol. 61:1639-1646; Adam, M.A. and A.D. Miller (1988) J. Virol. 62:3802-3806; Dull, T. et al. (1998) J. Virol. 72:8463-8471; Zufferey, R. et al. (1998) J. Virol. 72:9873-9880). U.S. Patent Number 5,910,434 to Rigg ("Method for obtaining retrovirus packaging cell lines producing high transducing efficiency retroviral supernatant") discloses a method for obtaining retrovirus packaging cell lines and is hereby incorporated by reference. Propagation of retrovirus vectors, transduction of a population of cells (e.g., CD4⁺ T-cells), and the return of transduced cells to a patient are procedures well known to persons skilled in the art of gene therapy and have been well documented (Ranga, U. et al. (1997) J. Virol. 71:7020-7029; Bauer, G. et al. (1997) Blood 89:2259-2267; Bonyhadi, M.L. (1997) J. Virol. 71:4707-4716; Ranga, U. et al. (1998) Proc. Natl. Acad. Sci. U.S.A. 95:1201-1206; Su, L. (1997) Blood 89:2283-2290).

In the alternative, an adenovirus-based gene therapy delivery system is used to deliver polynucleotides encoding INTRA to cells which have one or more genetic abnormalities with respect to the expression of INTRA. The construction and packaging of adenovirus-based vectors are well known to those with ordinary skill in the art. Replication defective adenovirus vectors have proven to be versatile for importing genes encoding immunoregulatory proteins into intact islets in the pancreas (Csete, M.E. et al. (1995) Transplantation 27:263-268). Potentially useful adenoviral vectors are described in U.S. Patent Number 5,707,618 to Armentano ("Adenovirus vectors for gene therapy"), hereby incorporated by reference. For adenoviral vectors, see also Antinozzi, P.A. et al. (1999) Annu. Rev. Nutr. 19:511-544; and Verma, I.M. and N. Somia (1997) Nature 389:239-242, both incorporated by reference herein.

In another alternative, a herpes-based, gene therapy delivery system is used to deliver polynucleotides encoding INTRA to target cells which have one or more genetic abnormalities with

respect to the expression of INTRA. The use of herpes simplex virus (HSV)-based vectors may be especially valuable for introducing INTRA to cells of the central nervous system, for which HSV has a tropism. The construction and packaging of herpes-based vectors are well known to those with ordinary skill in the art. A replication-competent herpes simplex virus (HSV) type 1-based vector has
5 been used to deliver a reporter gene to the eyes of primates (Liu, X. et al. (1999) *Exp. Eye Res.* 169:385-395). The construction of a HSV-1 virus vector has also been disclosed in detail in U.S. Patent Number 5,804,413 to DeLuca ("Herpes simplex virus strains for gene transfer"), which is hereby incorporated by reference. U.S. Patent Number 5,804,413 teaches the use of recombinant HSV d92 which consists of a genome containing at least one exogenous gene to be transferred to a
10 cell under the control of the appropriate promoter for purposes including human gene therapy. Also taught by this patent are the construction and use of recombinant HSV strains deleted for ICP4, ICP27 and ICP22. For HSV vectors, see also Goins, W.F. et al. (1999) *J. Virol.* 73:519-532 and Xu, H. et al. (1994) *Dev. Biol.* 163:152-161, hereby incorporated by reference. The manipulation of cloned herpesvirus sequences, the generation of recombinant virus following the transfection of multiple
15 plasmids containing different segments of the large herpesvirus genomes, the growth and propagation of herpesvirus, and the infection of cells with herpesvirus are techniques well known to those of ordinary skill in the art.

In another alternative, an alphavirus (positive, single-stranded RNA virus) vector is used to deliver polynucleotides encoding INTRA to target cells. The biology of the prototypic alphavirus,
20 Semliki Forest Virus (SFV), has been studied extensively and gene transfer vectors have been based on the SFV genome (Garoff, H. and K.-J. Li (1998) *Curr. Opin. Biotech.* 9:464-469). During alphavirus RNA replication, a subgenomic RNA is generated that normally encodes the viral capsid proteins. This subgenomic RNA replicates to higher levels than the full-length genomic RNA, resulting in the overproduction of capsid proteins relative to the viral proteins with enzymatic activity
25 (e.g., protease and polymerase). Similarly, inserting the coding sequence for INTRA into the alphavirus genome in place of the capsid-coding region results in the production of a large number of INTRA-coding RNAs and the synthesis of high levels of INTRA in vector transduced cells. While alphavirus infection is typically associated with cell lysis within a few days, the ability to establish a persistent infection in hamster normal kidney cells (BHK-21) with a variant of Sindbis virus (SIN)
30 indicates that the lytic replication of alphaviruses can be altered to suit the needs of the gene therapy application (Dryga, S.A. et al. (1997) *Virology* 228:74-83). The wide host range of alphaviruses will allow the introduction of INTRA into a variety of cell types. The specific transduction of a subset of cells in a population may require the sorting of cells prior to transduction. The methods of manipulating infectious cDNA clones of alphaviruses, performing alphavirus cDNA and RNA

transfections, and performing alphavirus infections, are well known to those with ordinary skill in the art.

Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, may also be employed to inhibit gene expression. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding INTRA.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding INTRA. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs

and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

5 An additional embodiment of the invention encompasses a method for screening for a compound which is effective in altering expression of a polynucleotide encoding INTRA. Compounds which may be effective in altering expression of a specific polynucleotide may include, but are not limited to, oligonucleotides, antisense oligonucleotides, triple helix-forming oligonucleotides, transcription factors and other polypeptide transcriptional regulators, and non-
10 macromolecular chemical entities which are capable of interacting with specific polynucleotide sequences. Effective compounds may alter polynucleotide expression by acting as either inhibitors or promoters of polynucleotide expression. Thus, in the treatment of disorders associated with increased INTRA expression or activity, a compound which specifically inhibits expression of the polynucleotide encoding INTRA may be therapeutically useful, and in the treatment of disorders
15 associated with decreased INTRA expression or activity, a compound which specifically promotes expression of the polynucleotide encoding INTRA may be therapeutically useful.

At least one, and up to a plurality, of test compounds may be screened for effectiveness in altering expression of a specific polynucleotide. A test compound may be obtained by any method commonly known in the art, including chemical modification of a compound known to be effective in
20 altering polynucleotide expression; selection from an existing, commercially-available or proprietary library of naturally-occurring or non-natural chemical compounds; rational design of a compound based on chemical and/or structural properties of the target polynucleotide; and selection from a library of chemical compounds created combinatorially or randomly. A sample comprising a polynucleotide encoding INTRA is exposed to at least one test compound thus obtained. The sample
25 may comprise, for example, an intact or permeabilized cell, or an *in vitro* cell-free or reconstituted biochemical system. Alterations in the expression of a polynucleotide encoding INTRA are assayed by any method commonly known in the art. Typically, the expression of a specific nucleotide is detected by hybridization with a probe having a nucleotide sequence complementary to the sequence of the polynucleotide encoding INTRA. The amount of hybridization may be quantified, thus
30 forming the basis for a comparison of the expression of the polynucleotide both with and without exposure to one or more test compounds. Detection of a change in the expression of a polynucleotide exposed to a test compound indicates that the test compound is effective in altering the expression of the polynucleotide. A screen for a compound effective in altering expression of a specific polynucleotide can be carried out, for example, using a *Schizosaccharomyces pombe* gene expression
35 system (Atkins, D. et al. (1999) U.S. Patent No. 5.932.435; Arndt, G.M. et al. (2000) Nucleic Acids

Res. 28:E15) or a human cell line such as HeLa cell (Clarke, M.L. et al. (2000) Biochem. Biophys. Res. Commun. 268:8-13). A particular embodiment of the present invention involves screening a combinatorial library of oligonucleotides (such as deoxyribonucleotides, ribonucleotides, peptide nucleic acids, and modified oligonucleotides) for antisense activity against a specific polynucleotide sequence (Bruice, T.W. et al. (1997) U.S. Patent No. 5,686,242; Bruice, T.W. et al. (2000) U.S. Patent No. 6,022,691).

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

An additional embodiment of the invention relates to the administration of a pharmaceutical composition which generally comprises an active ingredient formulated with a pharmaceutically acceptable excipient. Excipients may include, for example, sugars, starches, celluloses, gums, and proteins. Various formulations are commonly known and are thoroughly discussed in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA). Such pharmaceutical compositions may consist of INTRA, antibodies to INTRA, and mimetics, agonists, antagonists, or inhibitors of INTRA.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, pulmonary, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

Pharmaceutical compositions for pulmonary administration may be prepared in liquid or dry powder form. These compositions are generally aerosolized immediately prior to inhalation by the patient. In the case of small molecules (e.g. traditional low molecular weight organic drugs), aerosol delivery of fast-acting formulations is well-known in the art. In the case of macromolecules (e.g. larger peptides and proteins), recent developments in the field of pulmonary delivery via the alveolar region of the lung have enabled the practical delivery of drugs such as insulin to blood circulation (see, e.g., Patton, J.S. et al., U.S. Patent No. 5,997,848). Pulmonary delivery has the advantage of administration without needle injection, and obviates the need for potentially toxic penetration enhancers.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

Specialized forms of pharmaceutical compositions may be prepared for direct intracellular
5 delivery of macromolecules comprising INTRA or fragments thereof. For example, liposome preparations containing a cell-impermeable macromolecule may promote cell fusion and intracellular delivery of the macromolecule. Alternatively, INTRA or a fragment thereof may be joined to a short cationic N-terminal portion from the HIV Tat-1 protein. Fusion proteins thus generated have been found to transduce into the cells of all tissues, including the brain, in a mouse model system
10 (Schwarze, S.R. et al. (1999) Science 285:1569-1572).

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, monkeys, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and
15 routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example INTRA or fragments thereof, antibodies of INTRA, and agonists, antagonists or inhibitors of INTRA, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by
20 calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such
25 compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the
30 active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular
35 formulation.

Normal dosage amounts may vary from about 0.1 μg to 100,000 μg , up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

In another embodiment, antibodies which specifically bind INTRA may be used for the diagnosis of disorders characterized by expression of INTRA, or in assays to monitor patients being treated with INTRA or agonists, antagonists, or inhibitors of INTRA. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for INTRA include methods which utilize the antibody and a label to detect INTRA in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring INTRA, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of INTRA expression. Normal or standard values for INTRA expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, for example, human subjects, with antibody to INTRA under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of INTRA expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding INTRA may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of INTRA may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of INTRA, and to monitor regulation of INTRA levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding INTRA or closely related molecules may be used to identify nucleic acid sequences which encode INTRA. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification will determine whether the

probe identifies only naturally occurring sequences encoding INTRA, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the INTRA encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:53-104 or from genomic sequences including promoters, enhancers, and introns of the INTRA gene.

Means for producing specific hybridization probes for DNAs encoding INTRA include the cloning of polynucleotide sequences encoding INTRA or INTRA derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S , or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding INTRA may be used for the diagnosis of disorders associated with expression of INTRA. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, hematopoietic cancer including lymphoma, leukemia, and myeloma; and other cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, adenoma, carcinoma and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an autoimmune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal

circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma ; and a gastrointestinal disorder such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis, hyperbilirubinemia, cirrhosis, passive congestion of the liver, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, acquired immunodeficiency syndrome (AIDS) enteropathy, jaundice, hepatic encephalopathy, hepatorenal syndrome, hepatic steatosis, hemochromatosis, Wilson's disease, α_1 -antitrypsin deficiency, Reye's syndrome, primary sclerosing cholangitis, liver infarction, portal vein obstruction and thrombosis, centrilobular necrosis, peliosis hepatis, hepatic vein thrombosis, veno-occlusive disease, preeclampsia, eclampsia, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and a hepatic tumor including a nodular hyperplasia, a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, akathisia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; and a gastrointestinal disorder such as esophagitis, esophageal carcinoma, gastritis, gastric carcinoma, inflammatory bowel disease, cholecystitis, infections of the intestinal tract, pancreatitis, pancreatic carcinoma, cirrhosis, hepatitis, hepatoma, colitis, colonic carcinoma, and Crohn's disease. The polynucleotide sequences encoding

INTRA may be used in Southern or northern analysis, dot blot, or other membrane-based

technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered INTRA expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding INTRA may be useful in assays that
5 detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding INTRA may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to
10 a control sample then the presence of altered levels of nucleotide sequences encoding INTRA in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of
15 INTRA, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding INTRA, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified
20 polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the
25 patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the
30 development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding
35 INTRA may involve the use of PCR. These oligomers may be chemically synthesized, generated

enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding INTRA, or a fragment of a polynucleotide complementary to the polynucleotide encoding INTRA, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or
5 quantification of closely related DNA or RNA sequences.

In a particular aspect, oligonucleotide primers derived from the polynucleotide sequences encoding INTRA may be used to detect single nucleotide polymorphisms (SNPs). SNPs are substitutions, insertions and deletions that are a frequent cause of inherited or acquired genetic disease in humans. Methods of SNP detection include, but are not limited to, single-stranded
10 conformation polymorphism (SSCP) and fluorescent SSCP (fSSCP) methods. In SSCP, oligonucleotide primers derived from the polynucleotide sequences encoding INTRA are used to amplify DNA using the polymerase chain reaction (PCR). The DNA may be derived, for example, from diseased or normal tissue, biopsy samples, bodily fluids, and the like. SNPs in the DNA cause differences in the secondary and tertiary structures of PCR products in single-stranded form, and
15 these differences are detectable using gel electrophoresis in non-denaturing gels. In fSSCP, the oligonucleotide primers are fluorescently labeled, which allows detection of the amplimers in high-throughput equipment such as DNA sequencing machines. Additionally, sequence database analysis methods, termed *in silico* SNP (isSNP), are capable of identifying polymorphisms by comparing the sequence of individual overlapping DNA fragments which assemble into a common consensus
20 sequence. These computer-based methods filter out sequence variations due to laboratory preparation of DNA and sequencing errors using statistical models and automated analyses of DNA sequence chromatograms. In the alternative, SNPs may be detected and characterized by mass spectrometry using, for example, the high throughput MASSARRAY system (Sequenom, Inc., San Diego CA).

Methods which may also be used to quantify the expression of INTRA include radiolabeling
25 or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) *J. Immunol. Methods* 159:235-244; Duplaa, C. et al. (1993) *Anal. Biochem.* 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer or polynucleotide of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives
30 rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as elements on a microarray. The microarray can be used in transcript imaging techniques which monitor the relative expression levels of large numbers of genes simultaneously as described in Seilhamer, J.J. et al., "Comparative Gene Transcript
35 Analysis," U.S. Patent No. 5,840,484, incorporated herein by reference. The microarray may also be

used to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, to monitor progression/regression of disease as a function of gene expression, and to develop and monitor the activities of therapeutic agents in the treatment of disease. In particular, this information
5 may be used to develop a pharmacogenomic profile of a patient in order to select the most appropriate and effective treatment regimen for that patient. For example, therapeutic agents which are highly effective and display the fewest side effects may be selected for a patient based on his/her pharmacogenomic profile.

In another embodiment, antibodies specific for INTRA, or INTRA or fragments thereof may
10 be used as elements on a microarray. The microarray may be used to monitor or measure protein-protein interactions, drug-target interactions, and gene expression profiles, as described above.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al.
15 (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.) Various types of microarrays are well known and thoroughly described in DNA Microarrays: A Practical Approach, M. Schena, ed. (1999) Oxford University Press, London, hereby expressly incorporated by reference.

In another embodiment of the invention, nucleic acid sequences encoding INTRA may be
20 used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. Either coding or noncoding sequences may be used, and in some instances, noncoding sequences may be preferable over coding sequences. For example, conservation of a coding sequence among members of a multi-gene family may potentially cause undesired cross hybridization during chromosomal mapping. The sequences may be mapped to a particular chromosome, to a specific
25 region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.) Once mapped, the nucleic acid sequences of the invention may be
30 used to develop genetic linkage maps, for example, which correlate the inheritance of a disease state with the inheritance of a particular chromosome region or restriction fragment length polymorphism (RFLP). (See, e.g., Lander, E.S. and D. Botstein (1986) Proc. Natl. Acad. Sci. USA 83:7353-7357.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic
35 map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man

(OMIM) World Wide Web site. Correlation between the location of the gene encoding INTRA on a physical map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder and thus may further positional cloning efforts.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the exact chromosomal locus is not known. This information is valuable to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the gene or genes responsible for a disease or syndrome have been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the instant invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, INTRA, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between INTRA and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with INTRA, or fragments thereof, and washed. Bound INTRA is then detected by methods well known in the art. Purified INTRA can also be coated directly onto plates for use in the aforementioned drug screening techniques.

Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding INTRA specifically compete with a test compound for binding INTRA. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with INTRA.

In additional embodiments, the nucleotide sequences which encode INTRA may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

5 The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. 60/139,566 (filing date 16 June 1999), U.S. Ser. No. 60/149,640 (filing date 17 August 1999), and U.S. Ser. No. 60/164,417 (filing date 9 November 1999), are hereby expressly incorporated by reference.

10 EXAMPLES

I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a
15 monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated
20 using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA
25 libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERScript plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, *supra*, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the
30 appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUEScript plasmid (Stratagene), PSPOrt1 plasmid (Life Technologies), pcDNA2.1 plasmid
35 (Invitrogen, Carlsbad CA), or pINCY plasmid (Incyte Genomics, Palo Alto CA). Recombinant

plasmids were transformed into competent *E. coli* cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5 α , DH10B, or ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids obtained as described in Example I were recovered from host cells by *in vivo* excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

Incyte cDNA recovered in plasmids as described in Example II were sequenced as follows. Sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (PE Biosystems) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (PE Biosystems). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing system (PE Biosystems) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, *supra*, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example VI.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions, references, and threshold parameters. The first column of Table 5 shows the tools,

programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments were generated using the default parameters specified by the clustal algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programming, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and PFAM to acquire annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:53-104. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

IV. Analysis of Polynucleotide Expression

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in cDNA databases such as GenBank or LIFESEQ (Incyte Genomics). This analysis is

much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\text{BLAST Score} \times \text{Percent Identity}}{5 \times \text{minimum} \{ \text{length}(\text{Seq. 1}), \text{length}(\text{Seq. 2}) \}}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. The product score is a normalized value between 0 and 100, and is calculated as follows: the BLAST score is multiplied by the percent nucleotide identity and the product is divided by (5 times the length of the shorter of the two sequences). The BLAST score is calculated by assigning a score of +5 for every base that matches in a high-scoring segment pair (HSP), and -4 for every mismatch. Two sequences may share more than one HSP (separated by gaps). If there is more than one HSP, then the pair with the highest BLAST score is used to calculate the product score. The product score represents a balance between fractional overlap and quality in a BLAST alignment. For example, a product score of 100 is produced only for 100% identity over the entire length of the shorter of the two sequences being compared. A product score of 70 is produced either by 100% identity and 70% overlap at one end, or by 88% identity and 100% overlap at the other. A product score of 50 is produced either by 100% identity and 50% overlap at one end, or 79% identity and 100% overlap.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding INTRA occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation, trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

V. Chromosomal Mapping of ABBR Encoding Polynucleotides

The cDNA sequences which were used to assemble SEQ ID NO:8-14 were compared with sequences from the Incyte LIFESEQ database and public domain databases using BLAST and other implementations of the Smith-Waterman algorithm. Sequences from these databases that matched SEQ ID NO:8-14 were assembled into clusters of contiguous and overlapping sequences using assembly algorithms such as Phrap (Table 5). Radiation hybrid and genetic mapping data available from public resources such as the Stanford Human Genome Center (SHGC), Whitehead Institute for

Genome Research (WIGR), and Généthon were used to determine if any of the clustered sequences had been previously mapped. Inclusion of a mapped sequence in a cluster resulted in the assignment of all sequences of that cluster, including its particular SEQ ID NO., to that map location.

The genetic map locations of SEQ ID NO:8-14 [fill in the specific SEQ ID NOs if not all of the sequences have been mapped] are described in The Invention as ranges, or intervals, of human chromosomes. [Include the following sentence if any of your sequences have more than one map location.] More than one map location is reported for SEQ ID NO:8-14 [fill in specific SEQ ID NO:s], indicating that previously mapped sequences having similarity, but not complete identity, to SEQ ID NO:8-14 [fill in specific SEQ ID NO:s] were assembled into their respective clusters. The map position of an interval, in centiMorgans, is measured relative to the terminus of the chromosome's p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Généthon which provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters. Human genome maps and other resources available to the public, such as the NCBI "GeneMap'99" World Wide Web site (<http://www.ncbi.nlm.nih.gov/genemap/>), can be employed to determine if previously identified disease genes map within or in proximity to the intervals indicated above.

VI. Extension of INTRA Encoding Polynucleotides

The full length nucleic acid sequences of SEQ ID NO:53-104 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+} , $(NH_4)_2SO_4$, and β -mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C,

2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

5 The concentration of DNA in each well was determined by dispensing 100 µl PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 µl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the
10 concentration of DNA. A 5 µl to 10 µl aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

 The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and
15 sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site
20 overhangs, and transfected into competent *E. coli* cells. Transformed cells were selected on antibiotic-containing media, and individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

 The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following
25 parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethylsulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing
30 primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (PE Biosystems).

 In like manner, the polynucleotide sequences of SEQ ID NO:53-104 are used to obtain 5' regulatory sequences using the procedure above, along with oligonucleotides designed for such extension, and an appropriate genomic library.

35 **VII. Labeling and Use of Individual Hybridization Probes**

Hybridization probes derived from SEQ ID NO:53-104 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μ Ci of $[\gamma\text{-}^{32}\text{P}]$ adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10^7 counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and compared.

VIII. Microarrays

The linkage or synthesis of array elements upon a microarray can be achieved utilizing photolithography, piezoelectric printing (ink-jet printing, See, e.g., Baldeschweiler, *supra*), mechanical microspotting technologies, and derivatives thereof. The substrate in each of the aforementioned technologies should be uniform and solid with a non-porous surface (Skena (1999), *supra*). Suggested substrates include silicon, silica, glass slides, glass chips, and silicon wafers. Alternatively, a procedure analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced using available methods and machines well known to those of ordinary skill in the art and may contain any appropriate number of elements. (See, e.g., Skena, M. et al. (1995) *Science* 270:467-470; Shalon, D. et al. (1996) *Genome Res.* 6:639-645; Marshall, A. and J. Hodgson (1998) *Nat. Biotechnol.* 16:27-31.)

Full length cDNAs, Expressed Sequence Tags (ESTs), or fragments or oligomers thereof may comprise the elements of the microarray. Fragments or oligomers suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). The array elements are hybridized with polynucleotides in a biological sample. The polynucleotides in the biological sample are conjugated to a fluorescent label or other molecular tag for ease of detection. After hybridization, nonhybridized nucleotides from the biological sample are removed, and a

fluorescence scanner is used to detect hybridization at each array element. Alternatively, laser desorption and mass spectrometry may be used for detection of hybridization. The degree of complementarity and the relative abundance of each polynucleotide which hybridizes to an element on the microarray may be assessed. In one embodiment, microarray preparation and usage is described in detail below.

Tissue or Cell Sample Preparation

Total RNA is isolated from tissue samples using the guanidinium thiocyanate method and poly(A)⁺ RNA is purified using the oligo-(dT) cellulose method. Each poly(A)⁺ RNA sample is reverse transcribed using MMLV reverse-transcriptase, 0.05 pg/ μ l oligo-(dT) primer (21mer), 1X first strand buffer, 0.03 units/ μ l RNase inhibitor, 500 μ M dATP, 500 μ M dGTP, 500 μ M dTTP, 40 μ M dCTP, 40 μ M dCTP-Cy3 (BDS) or dCTP-Cy5 (Amersham Pharmacia Biotech). The reverse transcription reaction is performed in a 25 ml volume containing 200 ng poly(A)⁺ RNA with GEMBRIGHT kits (Incyte). Specific control poly(A)⁺ RNAs are synthesized by in vitro transcription from non-coding yeast genomic DNA. After incubation at 37 °C for 2 hr, each reaction sample (one with Cy3 and another with Cy5 labeling) is treated with 2.5 ml of 0.5M sodium hydroxide and incubated for 20 minutes at 85 °C to stop the reaction and degrade the RNA. Samples are purified using two successive CHROMA SPIN 30 gel filtration spin columns (CLONTECH Laboratories, Inc. (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated using 1 ml of glycogen (1 mg/ml), 60 ml sodium acetate, and 300 ml of 100% ethanol. The sample is then dried to completion using a SpeedVAC (Savant Instruments Inc., Holbrook NY) and resuspended in 14 μ l 5X SSC/0.2% SDS.

Microarray Preparation

Sequences of the present invention are used to generate array elements. Each array element is amplified from bacterial cells containing vectors with cloned cDNA inserts. PCR amplification uses primers complementary to the vector sequences flanking the cDNA insert. Array elements are amplified in thirty cycles of PCR from an initial quantity of 1-2 ng to a final quantity greater than 5 μ g. Amplified array elements are then purified using SEPHACRYL-400 (Amersham Pharmacia Biotech).

Purified array elements are immobilized on polymer-coated glass slides. Glass microscope slides (Corning) are cleaned by ultrasound in 0.1% SDS and acetone, with extensive distilled water washes between and after treatments. Glass slides are etched in 4% hydrofluoric acid (VWR Scientific Products Corporation (VWR), West Chester PA), washed extensively in distilled water, and coated with 0.05% aminopropyl silane (Sigma) in 95% ethanol. Coated slides are cured in a 110°C oven.

Array elements are applied to the coated glass substrate using a procedure described in US Patent No. 5,807,522, incorporated herein by reference. 1 μ l of the array element DNA, at an average concentration of 100 ng/ μ l, is loaded into the open capillary printing element by a high-speed robotic apparatus. The apparatus then deposits about 5 nl of array element sample per slide.

5 Microarrays are UV-crosslinked using a STRATALINKER UV-crosslinker (Stratagene). Microarrays are washed at room temperature once in 0.2% SDS and three times in distilled water. Non-specific binding sites are blocked by incubation of microarrays in 0.2% casein in phosphate buffered saline (PBS) (Tropix, Inc., Bedford MA) for 30 minutes at 60 °C followed by washes in 0.2% SDS and distilled water as before.

10 Hybridization

Hybridization reactions contain 9 μ l of sample mixture consisting of 0.2 μ g each of Cy3 and Cy5 labeled cDNA synthesis products in 5X SSC, 0.2% SDS hybridization buffer. The sample mixture is heated to 65 °C for 5 minutes and is aliquoted onto the microarray surface and covered with an 1.8 cm² coverslip. The arrays are transferred to a waterproof chamber having a cavity just
15 slightly larger than a microscope slide. The chamber is kept at 100% humidity internally by the addition of 140 μ l of 5X SSC in a corner of the chamber. The chamber containing the arrays is incubated for about 6.5 hours at 60 °C. The arrays are washed for 10 min at 45 °C in a first wash buffer (1X SSC, 0.1% SDS), three times for 10 minutes each at 45 °C in a second wash buffer (0.1X SSC), and dried.

20 Detection

Reporter-labeled hybridization complexes are detected with a microscope equipped with an Innova 70 mixed gas 10 W laser (Coherent, Inc., Santa Clara CA) capable of generating spectral lines at 488 nm for excitation of Cy3 and at 632 nm for excitation of Cy5. The excitation laser light is focused on the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide
25 containing the array is placed on a computer-controlled X-Y stage on the microscope and raster-scanned past the objective. The 1.8 cm x 1.8 cm array used in the present example is scanned with a resolution of 20 micrometers.

In two separate scans, a mixed gas multiline laser excites the two fluorophores sequentially. Emitted light is split, based on wavelength, into two photomultiplier tube detectors (PMT R1477,
30 Hamamatsu Photonics Systems, Bridgewater NJ) corresponding to the two fluorophores. Appropriate filters positioned between the array and the photomultiplier tubes are used to filter the signals. The emission maxima of the fluorophores used are 565 nm for Cy3 and 650 nm for Cy5. Each array is typically scanned twice, one scan per fluorophore using the appropriate filters at the laser source, although the apparatus is capable of recording the spectra from both fluorophores simultaneously.

The sensitivity of the scans is typically calibrated using the signal intensity generated by a cDNA control species added to the sample mixture at a known concentration. A specific location on the array contains a complementary DNA sequence, allowing the intensity of the signal at that location to be correlated with a weight ratio of hybridizing species of 1:100,000. When two samples from different sources (e.g., representing test and control cells), each labeled with a different fluorophore, are hybridized to a single array for the purpose of identifying genes that are differentially expressed, the calibration is done by labeling samples of the calibrating cDNA with the two fluorophores and adding identical amounts of each to the hybridization mixture.

The output of the photomultiplier tube is digitized using a 12-bit RTI-835H analog-to-digital (A/D) conversion board (Analog Devices, Inc., Norwood MA) installed in an IBM-compatible PC computer. The digitized data are displayed as an image where the signal intensity is mapped using a linear 20-color transformation to a pseudocolor scale ranging from blue (low signal) to red (high signal). The data is also analyzed quantitatively. Where two different fluorophores are excited and measured simultaneously, the data are first corrected for optical crosstalk (due to overlapping emission spectra) between the fluorophores using each fluorophore's emission spectrum.

A grid is superimposed over the fluorescence signal image such that the signal from each spot is centered in each element of the grid. The fluorescence signal within each element is then integrated to obtain a numerical value corresponding to the average intensity of the signal. The software used for signal analysis is the GEMTOOLS gene expression analysis program (Incyte).

IX. Complementary Polynucleotides

Sequences complementary to the INTRA-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring INTRA. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of INTRA. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the INTRA-encoding transcript.

X. Expression of INTRA

Expression and purification of INTRA is achieved using bacterial or virus-based expression systems. For expression of INTRA in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory

element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express INTRA upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of INTRA in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding INTRA by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, INTRA is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from INTRA at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch. 10 and 16). Purified INTRA obtained by these methods can be used directly in the assays shown in Examples XI, XII, and XV.

XI. Demonstration of INTRA Activity

INTRA activity is associated with its ability to form protein-protein complexes and is measured by its ability to regulate growth characteristics of NIH3T3 mouse fibroblast cells. A cDNA encoding INTRA is subcloned into an appropriate eukaryotic expression vector. This vector is transfected into NIH3T3 cells using methods known in the art. Transfected cells are compared with non-transfected cells for the following quantifiable properties: growth in culture to high density, reduced attachment of cells to the substrate, altered cell morphology, and ability to induce tumors when injected into immunodeficient mice. The activity of INTRA is proportional to the extent of increased growth or frequency of altered cell morphology in NIH3T3 cells transfected with INTRA.

Alternatively, INTRA activity is measured by binding of INTRA to radiolabeled formin polypeptides containing the proline-rich region that specifically binds to SH3 containing proteins

(Chan, D.C. et al. (1996) EMBO J. 15: 1045-54). Samples of INTRA are run on SDS-PAGE gels, and transferred onto nitrocellulose by electroblotting. The blots are blocked for 1 hr at room temperature in TBST (137 mM NaCl, 2.7 mM KCl, 25 mM Tris (pH 8.0) and 0.1% Tween-20) containing non-fat dry milk. Blots are then incubated with TBST containing the radioactive formin polypeptide for 4 hrs to overnight. After washing the blots four times with TBST, the blots are exposed to autoradiographic film. Radioactivity is quantitated by cutting out the radioactive spots and counting them in a radioisotope counter. The amount of radioactivity recovered is proportional to the activity of INTRA in the assay.

Alternatively, INTRA activity is demonstrated by measuring the binding of INTRA to Ca^{2+} using a Ca^{2+} overlay system (Weis, K. et al. (1994) J. Biol. Chem. 269:19142-19150). Purified INTRA is transferred and immobilized onto a nitrocellulose membrane. The membrane is washed three times with buffer (60 mM KCl, 5 mM MgCl_2 , 10 mM imidazole-HCl, pH 6.8) and incubated in this buffer for 10 minutes with 1 μCi [$^{45}\text{Ca}^{2+}$] (NEN-DuPont, Boston, MA). Unbound [$^{45}\text{Ca}^{2+}$] is removed from the membrane by washing with water, and the membrane is dried. Membrane-bound [$^{45}\text{Ca}^{2+}$] is detected by autoradiography and quantified using image analysis systems and software. INTRA activity is proportional to the amount of [$^{45}\text{Ca}^{2+}$] detected on the membrane.

Alternatively, INTRA activity is assayed by measuring the conversion of ^3H -cAMP to ^3H -adenosine in the presence of INTRA and 5' nucleotidase. INTRA is added to a solution containing 50 mM Tris-HCl pH 7.5, 10 mM MgCl_2 , 0.1 unit 5' nucleotidase (from *Crotalus atrox* venom), and 0.0064-2.0 μM ^3H -cAMP and the reaction is incubated at 37°C for a time period that would yield less than 15% cAMP hydrolysis in order to avoid non-linearity associated with product inhibition. Soluble radioactivity associated with ^3H -adenosine is quantitated using a Beta scintillation counter. The amount of radioactivity recovered is proportional to the activity of INTRA in the reaction.

XII. Functional Assays

INTRA function is assessed by expressing the sequences encoding INTRA at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT plasmid (Life Technologies) and pCR3.1 plasmid (Invitrogen), both of which contain the cytomegalovirus promoter. 5-10 μg of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2 μg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP;

Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of INTRA on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding INTRA and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding INTRA and other genes of interest can be analyzed by northern analysis or microarray techniques.

XIII. Production of INTRA Specific Antibodies

INTRA substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the INTRA amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (PE Biosystems) using FMOC chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-INTRA activity by, for example, binding the peptide or INTRA to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIV. Purification of Naturally Occurring INTRA Using Specific Antibodies

Naturally occurring or recombinant INTRA is substantially purified by immunoaffinity chromatography using antibodies specific for INTRA. An immunoaffinity column is constructed by covalently coupling anti-INTRA antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing INTRA are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of INTRA (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/INTRA binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and INTRA is collected.

XV. Identification of Molecules Which Interact with INTRA

INTRA, or biologically active fragments thereof, are labeled with ¹²⁵I Bolton-Hunter reagent. (See, e.g., Bolton A.E. and W.M. Hunter (1973) *Biochem. J.* 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled INTRA, washed, and any wells with labeled INTRA complex are assayed. Data obtained using different concentrations of INTRA are used to calculate values for the number, affinity, and association of INTRA with the candidate molecules.

Alternatively, molecules interacting with INTRA are analyzed using the yeast two-hybrid system as described in Fields, S. and O. Song (1989, *Nature* 340:245-246), or using commercially available kits based on the two-hybrid system, such as the MATCHMAKER system (Clontech).

INTRA may also be used in the PATHCALLING process (CuraGen Corp., New Haven CT) which employs the yeast two-hybrid system in a high-throughput manner to determine all interactions between the proteins encoded by two large libraries of genes (Nandabalan, K. et al. (2000) U.S. Patent No. 6,057,101).

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

Table 1

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	53	129042	TESTNOT01	129042H1 (TESTNOT01), 129042T6 (TESTNOT01), 594163H1 (BRAVUNT02), 1376353T6 (LUNGNOT10), 1968641R6 (BRSTNOT04), 4193335F6 (BRAPDIT01), 5636985H1 (UTRSTMR01)
2	54	778003	COLNNOT05	778003H1 (COLNNOT05), 778003X29 (COLNNOT05), 793138X17 (PROSTUT03), 5533562H1 (HEARFET05)
3	55	1418671	KIDNNOT09	458013F1 (KERANOT01), 461367R6 (KERANOT01), 1418671H1 (KIDNNOT09), 1418671X301D1 (KIDNNOT09), 1452670F1 (PENITUT01), 1455886F1 (COLNFET02), 2921431H1 (SININOT04)
4	56	1456841	COLNFET02	214180X3 (STOMNOT01), 1456841H1 (COLNFET02), 1517021F1 (PANCUTUT01), 2280709F6 (COLSUCT01), SBFA01757F1, SBFA04860F1, SBFA03431F1
5	57	2020010	CONNNOT01	520251R1 (MLR2DT01), 552501H1 (SCORNOT01), 1297508H1 (BRSTNOT07), 1417085H1 (BRAINOT12), 1455946F1 (COLNFET02), 1864670H1 (PROSNOT19), 1922941R6 (BRSTTUT01), 1922941T6 (BRSTTUT01), 1930785H1 (COLNTUT03), 2020010F6 (CONNNOT01), 2020010H1 (CONNNOT01), 2879789H1 (UTRSTUT05), 3324110H1 (PTHYNOT03), 3766286H1 (BRSTNOT24), 4305754H1 (TESTTUT03)
6	58	2149037	BRAINOT09	1382860F1 (BRAITUT08), 1709135F6 (PROSNOT16), 1758155R6 (PITUNOT03), 1861076F6 (PROSNOT19), 2149037H1 (BRAINOT09), 2149037X15F1 (BRAINOT09), 2280366H1 (PROSNON01), 2524642F6 (BRAITUT21), 2590271H1 (LUNGNOT22), 2970418H2 (HEAONOT02), 3084127H1 (BRAIFET01), 4789892T6 (EPIBUNT01)
7	59	2162179	ENDCNOT02	2162179F6 (ENDCNOT02), 2162179H1 (ENDCNOT02), 3865236H1 (BRAITUT07)
8	60	2244706	HIPONON02	2244706H1 (HIPONON02), 3272168F6 (BRAINOT20), SBWA00950V1, SBWA03641V1, SBWA02322V1

Table 1 (cont.)

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
9	61	2316805	OVARNOT02	363271R6 (PROSNOT01), 855363H1 (NGANNOT01), 1209030T1 (BRSTNOT02), 1265148R1 (SYNORAT05), 1294807F1 (PGANNOT03), 1351585F1 (LATRTUT02), 1852006F6 (LUNGFET03), 2316805H1 (OVARNOT02), 2320867H1 (OVARNOT02), 3563231F6 (SKINNOT05)
10	62	2320010	OVARNOT02	448783H1 (TYMNOT02), 470134R1 (MMLR1DT01), 720124F1 (SYNOAT01), 1873477F6 (LEUKNOT02), 2320010H1 (OVARNOT02), 3049510T6 (LUNGNOT25), 3087109F6 (HEAONOT03), 4144881H1 (SINITUT04), 5089346H1 (UTRSTMR01)
11	63	2564901	ADRETUT01	214410F1 (STOMNOT01), 927356R1 (BRAINOT04), 2564901H1 (ADRETUT01)
12	64	2615168	GBLANOT01	1445950F6 (PLACNOT02), 2615168H1 (GBLANOT01), 2746963F6 (LUNGUTUT11), 2746963T6 (LUNGUTUT11), 3250984H1 (SEMVNOT03), 3459378H1 (293TF1T01), 3831615H1 (PANCNOT17), 4334378H1 (KIDCTMT01), 4818908H1 (PROSTUT17)
13	65	2658329	LUNGUTUT09	1210539H1 (BRSTNOT02), 1210539R6 (BRSTNOT02), 1985147R6.comp (LUNGAST01), 2311120R6 (NGANNOT01), 2658329H1 (LUNGUTUT09), 2717243F6 (THYRNOT09), 2831384F7 (TYMNOT03), 3846358H1 (DENDNOT01), 4898171H1 (OVARDIT01)
14	66	2708944	PONSAZT01	309840R6 (TMLR2DT01), 1241166R6 (LUNGNOT03), 1381850H1 (BRAITUT08), 2194624F6 (THYRTUT03), 2212407F6 (SINTFET03), 2708944F6 (PONSAZT01), 2708944H1 (PONSAZT01), 4895659H1 (LIVRTUT12)
15	67	3315012	293TF1T01	532568R6 (BRAINOT03), 1300242F1 (BRSTNOT07), 1329265F1 (PANCNOT07), 1439786H1 (PANCNOT08), 2327916X23C1 (COLNNOT11), 2381037X37C1 (ISLTNOT01), 2381037X39C1 (ISLTNOT01), 3315012H1 (293TF1T01), SAEB00241R1
16	68	4155412	ADRENOT14	555524R6 (SCORNOT01), 4155412F6 (ADRENOT14), 4155412H1 (ADRENOT14), 4943387F6 (BRAIFEN05)

Table 1 (cont.)

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
17	69	4831840	BRAVXTXT03	286660H1 (EOSIHET02), 422026H1 (CARCTX01), 1734445F6 (COLNNOT22), 1734445T6 (COLNNOT22), 1970421F6 (UCMCL5T01), 2512308H1 (CONUTUT01), 4831840H1 (BRAVXTXT03)
18	70	5676581	293TF2T01	702633R6 (SYNORAT03), 1000026R1 (BRSTNOT03), 2631308F6 (COLNTUT15), 3012653H1 (MUSCNOT07), 3252744H1 (OVRTUN01), 3315168H2 (293TF2T01), 3530354H1 (BLADNOT09), 4289137H1 (BRABDIR01), 4974749H1 (HELATXT03), 5676581H1 (293TF2T01)
19	71	034159	THP1NOB01	034159H1 (THP1NOB01), 034159X305D3 (THP1NOB01), 406358R6 (EOSIHET02), 1974550F6 (UCMCL5T01), 3471911H1 (LUNGNOT27), 3522363H1 (ESOGTUN01), 4326520H1 (TLYMUNT01), SCJA01020V1, SCJA01764V1
20	72	129023	TESTNOT01	129023R6 (TESTNOT01), 775480R1 (COLNNOT05), 1649938F6 (PROSTUT09), 2518140F6 (BRAITUT21), 2688123H1 (LUNGNOT23), 4306520H1 (MONOTXT01)
21	73	1358940	LUNGNOT09	879273R1 (THYRNOT02), 967670T1 (BRSTNOT05), 1358940F6 (LUNGNOT09), 1358940H1 (LUNGNOT09), 1809259H1 (PROSTUT12), 1818790F6 (PROSNOT20), 1886716F6 (BLADTUT07), 1905126F6 (OVARNOT07), 3508881H1 (CONCNOT01), 3687018F6 (HEAANOT01), 3812474F6 (TONSNOT03)
22	74	1682320	PROSNOT15	1214001T1 (BRSTTUT01), 1259957F1 (MENITUT03), 1375132H1 (LUNGNOT10), 1682320H1 (PROSNOT15), 3137047H1 (SMCCNOT01), 3805984H1 (BLADTUT03), 3806302H1 (BLADTUT03)
23	75	1728263	PROSNOT14	1269315H1 (BRAINOT09), 1453910F1 (PENITUT01), 1728263H1 (PROSNOT14), g2115530
24	76	1867626	SKINBIT01	667711T6 (SCORNOT01), SXYA01116V1, SXYA01833V1, SXYA02442V1

Table 1 (cont.)

25	77	1990126	CORPNOT02	426763T6 (BLADNOT01), 1647316F6 (PROSTUT09), 1757430R6 (PITUNOT03), 1830621F6 (THP1AZT01), 1990126H1 (CORPNOT02), 3250740H1 (SEMVNOT03)
26	78	2104180	BRAITUT02	1350750F1 (LATRTUT02), 1502445F1 (BRAITUT07), 1519125X301D1 (BLADTUT04), 2104180H1 (BRAITUT02), 2733677H1 (OVARUTUT04)
27	79	2122241	BRSTNOT07	1402761H1 (LATRTUT02), 1402761T6 (LATRTUT02), 2122241F6 (BRSTNOT07), 2122241H1 (BRSTNOT07), 4989861H1 (LIVRTUT11)
28	80	2580428	KIDNTUT13	157262F1 (THP1PLB02), 1914234X29C1 (PROSTUT04), 1914467X12C1 (PROSTUT04), 1914467X13C1 (PROSTUT04), 1915166X14C1 (PROSTUT04), 2580428H1 (KIDNTUT13), SKA01222F1
29	81	3397189	UTRSNOT16	759108R6 (BRAITUT02), 1911587T6 (CONNTUT01), 3397189H1 (UTRSNOT16)
30	82	4881249	UTRMTMT01	080470R1 (SYNORAB01), 998242R6 (KIDNTUT01), 4549519H1 (HELAUNT01), 4881249H1 (UTRMTMT01), SXA01512V1, SXA02289V1, SXA00433V1
31	83	431871	EOSINOT03	431871H1 (BRAVUNT02), 460185R1 (KERANOT01), 636514F1 (NEUTGMT01), 1975990T6 (PANCUTUT02), 2212046H1 (SINTFET03), 2257310R6 (OVARUT01), 2300180R6 (BRSTNOT05), 4884920F6 (LUNLTMT01), SCEA00887V1
32	84	526155	EOSINOT02	526155H1 (EOSINOT02), 794168R6 (OVARNOT03), 1260927R1 (SYNORAT05), 1975556F6 (PANCUTUT02), 5157385H1 (BRSTTMT02)
33	85	676234	CRBLNOT01	676234H1 (CRBLNOT01), 2241232F6 (PANCUTUT02), 2241232T6 (PANCUTUT02), 2824092H1 (ADRETUT06), 4248435T6 (BRABDIT01)
34	86	720145	SYNOOAT01	433978H1 (THYRNOT01), 720145H1 (SYNOOAT01), 720145R6 (SYNOOAT01), 2107540T6 (BRAITUT03), 4722278H1 (COLCTUT02)
35	87	1001951	BRSTNOT03	1001951H1 (BRSTNOT03), 1001951R6 (BRSTNOT03), SXYA00708V1, SXYA01879V1, SXYA00520V1, SXYA00731V1, SXYA00926V1
36	88	1243349	LUNGNOT03	050083X316F1 (CHAONOT01), 050083X326F1 (CHAONOT01), 050083X346F1 (CHAONOT01), 050083X350F1 (CHAONOT01), 1243349H1 (LUNGNOT03), 2751089R6 (THP1AZS08), 3773254F6 (BRSTNOT25), 3997530H1 (PROSBPS05), g8443357, g1940784, g4539083

Table 1 (cont.)

37	89	1338201	COLNNOT13	256461H1 (HNT2RAT01), 1338201H1 (COLNNOT13), 1338201X12 (COLNNOT13), 1338201X18 (COLNNOT13), 1338201X21 (COLNNOT13), 2078127H1 (ISLTNOT01), g777838, g1146680, g1406379
38	90	1405141	LATRTUT02	189682R6 (CARDNOT01), 551762R6 (SCORNOT01), 1405141X302D1 (LATRTUT02), 1459886X16C1 (COLNFET02), 2601416H1 (UTRSNOT10), 2836108H2 (TLYMNOT03), 3031895F6 (TLYMNOT05), 3127628H1 (LUNGUTUT12), 3402733H1 (ESOGNOT03), 4289784F6 (BRABDIR01), 4339406H1 (BRAUNOT02), 4712515H1 (BRAIHCT01), 4746879H2 (SMCRUNT01), 5091792F6 (UTRSTMR01), 5679882H1 (BRAENOT02), 5927661H1 (BRAIFET02)
39	91	1686305	PROSNOT15	499154R6 (NEUTLPT01), 1686305F6 (PROSNOT15), 1686305H1 (PROSNOT15), 2306450R6 (NGANNOT01), 2446232F6 (THP1NOT03), 2446232T6 (THP1NOT03), 3050482H1 (LUNGNOT25), 3694303F6 (LUNGNOT35), 3825239H1 (BRAIHCT01), 3931022H1 (PROSTUT09), 4383527H1 (BRAVUTT02)
40	92	1688972	PROSTUT10	878019H1 (LUNGAST01), 1255436F2 (MENITUT03), 1330287F1 (PANCNOT07), 1400064F6 (BRAITUT08), 1688972H1 (PROSTUT10), 2018742F6 (THP1NOT01), 2047754X12F1 (SININOT01), 3002925H1 (TLYMNOT06), 3744192H1 (THYMNOT08)
41	93	1812494	PROSTUT12	1322590F6 (BLADNOT04), 1684555F6 (PROSNOT15), 2120930H1 (BRSTNOT07), 2266093H1 (UTRSNOT02), 2631470F6 (COLNUTUT15), 3980110H1 (LUNGUTUT08), 5115462H1 (ENDITXT01), SADA00912R1
42	94	2013853	TESTNOT03	2013853H1 (TESTNOT03), 2013853R6 (TESTNOT03), SXBC01227V1, SCSA04222V1
43	95	2284925	BRAINON01	464655X11 (LATRNOT01), 464655X12 (LATRNOT01), 464655X28 (LATRNOT01), 482019X21 (HNT2RAT01), 1443611R1 (THYRNOT03), 1443611X22 (THYRNOT03), 2284925H1 (BRAINON01), 2882173F6 (UTRSTUT05), 3485205F6 (KIDNNOT31), 3485205T6 (KIDNNOT31), SAAB00144R1

Table 1 (cont.)

44	ISLTNOT01	2376728	96	413593R6 (BRSTNOT01), 823803R1 (PROSNOT06), 860037R1 (BRAITUT03), 1282102F1 (COLNNOT16), 1733518F6 (BRSTTUT08), 2376728F6 (ISLTNOT01), 2376728H1 (ISLTNOT01), 2937285F6 (THYMFET02), 3108296H1 (BRSTTUT15), 3212546H1 (BLADNOT08), 3462704H1 (293TF2T01)
45	COLNTUT16	2790762	97	126628F1 (LUNGNOT01), 126628R1 (LUNGNOT01), 2790762F6 (COLNTUT16), 2790762H1 (COLNTUT16), 4002872H1 (HNT2AZS07), 9678705
46	THYRNOT10	2869164	98	1607765F6 (LUNGNOT15), 2869164F6 (THYRNOT10), 2869164H1 (THYRNOT10), 2869164T6 (THYRNOT10), 2890205H1 (LUNGFET04), 2891521F6 (LUNGFET04), 3094580X305D1 (CERVNOT03)
47	PROSBPT03	3317629	99	3166243H1 (SATABT007), 3317629F6 (PROSBPT03), 3421114X302F1 (UCMCNOT04), 4635773F6 (MYEPTXT01), 4635773T6 (MYEPTXT01)
48	BMARNOT03	3870488	100	1670688F6 (BMARNOT03), 3039406T6 (BRSTNOT16), 3870488H1 (BMARNOT03), 4773630H1 (BRAQNOT01)
49	UTRSNOT05	3886318	101	198182F1 (KIDNNOT02), 474711R1 (MMLRIDT01), 733227R1 (LUNGNOT03), 1236870F1 (LUNGFET03), 1502818F1 (BRAITUT07), 3742588H1 (THYMNOT08)
50	LUNGNOT35	4043934	102	4043934F6 (LUNGNOT35), 4043934H1 (LUNGNOT35), g1664159, g2114678, g3665589
51	THYMNOT11	4371445	103	4371445F6 (THYMNOT11), 4371445H1 (THYMNOT11), 4371445T6 (THYMNOT11), g691417
52	KIDNNOT34	5527925	104	878842R1 (THYRNOT02), 1662614F6 (BRSTNOT09), 1820183F6 (GBLATUT01), 2275208H1 (PROSNOT01), 2864564H1 (KIDNNOT20), 2890511H1 (LUNGFET04), 4312193H1 (BRAFNOT01), 5175111F6 (EPIBTXT01), 5876074H1 (BRAUNOT01)

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences and Motifs	Homologous Sequences	Analytical Methods and Databases
1	446	T24 T144 S251 S384 S404 T114 T118 T121 T172 S181 S247 Y53 Y422	N117 N232	SH3 domain: E387-I441	g2232009, thyroid hormone responsive protein [Rattus norvegicus]. Shah, G.N. et al. (1997) Biochem. J. 327:617-23.	BLAST - GenBank BLAST - DOMO BLIMPS - BLOCKS BLIMPS - PRINTS HMMER - PFAM MOTIFS
2	340	T26 S51 T146 S211 S270 S308 S73 S277 S317 Y71		SH2 domain: W240-Y316	g3738265 SH2 domain- containing protein [Mus musculus]	BLAST - GenBank BLAST - DOMO BLIMPS - PRINTS HMMER - PFAM MOTIFS
3	353	T45 S232 T353 T78 S88 S163 S176 T222 S240 S284 S302 T326 S338 S116 S120 T154 S226 S295 S337		Pleckstrin homology domains: T247-T353 G4-H104 S120-K250	g5381422 pleckstrin 2 [Homo sapiens]	BLAST - GenBank BLAST - PRODOM HMMER - PFAM MOTIFS
4	593	S230 S415 T84 T115 S214 S231 S309 S355 S372 T377 T387 S529 S580 S5 T36 S41 S90 S205 T263 S264 T343 T371 S410 S445 S483 S528 T547	N19 N542	SH3 domain: L453-L507 EPS8 region - SH3/phosphorylation domain: S2-P395	g309217 Eps8 (EGF receptor kinase substrate) [Mus musculus]	BLAST - GenBank BLAST - PRODOM HMMER - PFAM MOTIFS

Table 2

5	358	T42 S82 T204 T233 S261 T271 T279 S285 S330 S55 T102 S153 S254 S353	N338	Ankyrin repeat: G40-G67	g485107 similar to ankyrin repeat region [C. elegans]	BLAST - GenBank HMMER - PFAM MOTIFS
6	749	S137 T401 S406 T407 S580 T29 S140 S148 S149 S287 T336 S342 S360 S511 S551 T627 T29 S104 T368 S480 T616 Y141 Y303	N147 N392 N453 N640	Transmembrane domain: W280-I297 SH3 domain: R483-L537 Probable rabGAP domains: I159-P168 Y200-G205	g1519685 contains similarity to SH3 domains [C. elegans].	BLAST - GenBank BLIMPS - PRINTS BLIMPS - PFAM HMMER - PFAM HMMER MOTIFS
7	139	T51 T113 S106	N31		g169306 calmodulin [Phytophthora infestans]	BLAST - GenBank
8	539	S52 S84 T114 S186 S430 T468 S15 S110 S241 S307 S309 S353 S362 S363 S389 S485 S118 S169 S181 S210 T319 S385 T434 T523 Y208 Y305	N533	Pleckstrin homology domain: R192-A291	g4151807 membrane- associated guanylate kinase- interacting protein 2 (Maguin-2) [Rattus norvegicus]	BLAST - GenBank HMMER - PFAM MOTIFS
9	319	S169 S214 S233 S240 S150	N126	Tumor necrosis factor and nerve growth factor receptors - Conserved domain containing six cysteines: L166-C204	g2809400 Sprouty 2 (antagonist of FGF signaling) [Homo sapiens]	BLAST - GenBank HMMER - PFAM MOTIFS

Table 2 (cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences and Motifs	Homologous Sequences	Analytical Methods and Databases
10	747	T194 T344 T561 S655 S45 T58 T60 T74 T81 T171 S287 T294 S446 T526 S608 T610 T733 S126 S133 T165 S170 T190 S234 T251 T429 S470 S492 T522 S546 S735 S741 Y504 Y543	N32 N54 N533 N642		g550420 trg (transcript negatively regulated by thyroid stimulating hormone) [Rattus norvegicus]	
11	266	S62 T76 T183 S222 S4 T5 S256 S260 Y179	N47	Diacylglycerol/phorbol ester binding domain: E177-N223		PROFILESAN HMMER - PFAM MOTIFS
12	345	T87 S131 S213 T241 S299 S323 T34 T69 T223 S307	N40 N70	Annexin domain: G58-L110 L122-R143 I137-L182 L262-F316 E311-D326 A327-C340	g3688370, annexin 31 (annexin XXXI) [Homo sapiens]. Morgan, R.O. and Fernandez, M.P. (1998) FEBS Lett. 434:300-304.	BLAST - GenBank HMMER - PFAM BLIMPS - BLOCKS BLIMPS - PRINTS MOTIFS
13	437	S40 T66 T79 S93 T241 T289 S305 S342 T375 S47 S270 S362 T371 T393			<u>g685183</u> NGD5 gene product (regulated by opioid treatment) [Murinae gen. sp.]	BLAST - GenBank MOTIFS

Table 2 (cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences and Motifs	Homologous Sequences	Analytical Methods and Databases
14	441	S333 S419 T10 T24 T322 S403 S407 S422 T453 S33 S270 S329 T352 S487		Ankyrin repeats: G46-N73 G80-D107	<u>g6460678</u> ankyrin-related protein [Deinococcus radiodurans].	BLAST - GenBank HMMER - PFAM MOTIFS
15	487	S31 T51 S62 T220 T237 T254 T427 S453 T471 S482 T483 T95 S182	N242 N481	Signal peptide: M1-A28 Histidine acid phosphatase domains: R88-T95 K311-W323 Acid phosphatase-like region: E75-S484	<u>g4105496</u> multiple inositol polyphosphate phosphatase [Mus musculus].	BLAST - GenBank BLAST - PRODOM BLIMPS - BLOCKS HMMER SPSCAN MOTIFS
16	282	S25 T125 T157 T203 S31 S46 S107 S133 S194 S218 S257	N17 N74 N216		<u>g688297</u> VDUP1 (1,25- dihydroxy- vitamin D-3 up- regulated polypeptide [Homo sapiens].	BLAST - GenBank MOTIFS
17	581	T147 T327 S477 S41 T119 T123 T129 T209 S232 S243 S257 S299 S341 S347 T366 S371 S142 S220 S223 S237 S276 S323 S399 T472 T487 S518	N221 N358		g6013191 , activating signal cointegrator 1 [H. sapiens]. Kim, H.J. et al. (1999) Mol. Cell. Biol. 19:6323-6332.	BLAST - GenBank MOTIFS

Table 2 (cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences and Motifs	Homologous Sequences	Analytical Methods and Databases
18	530	S23 T46 S219 S221 T267 T268 S290 S303 T370 T382 S406 S446 T2 S31 S195 S339 S358 T375 S379 S399 T424 T445 T504	N43 N99	Signal peptide: M1-S23 WW/rsp5/WWP repeat domain: E123-P153 Trehalase domains: P80-T90 E129-N142	g1255031 FBP 30 (formin binding protein 30) [Mus musculus]	BLAST - GenBank SPSCAN HMMER - PFAM BLIMPS - BLOCKS MOTIFS
19 (034159)	475	S264 T5 T9 S33 S163 S171 S211 S217 S241 T267 S343 S370 T386 S472 S16 S110 S111 S151 S152 S246 T260 S264 T405	N15 N62 N101 N291 N384 N443	Pleckstrin M79-D189 GTPase activator K248- A459	g35013 n-chimaerin	Motifs BLAST_GENBANK HMMER_PFAM BLIMPS_PRINTS BLIMPS_PFAM BLAST_PRODROM BLAST_DOMO
20 (129023)	368	S8 S54 S70 S99 T158 S159 S253 S361 S30 T152 S308	N24 N68 N359	Signal peptide: M1-Q25 WW (signal transduction associated) domain: Y61-P75		Motifs SPSCAN BLIMPS_PRINTS
21 (1358940)	476	S104 S182 T343 S122 T148 T157 T197 S205 T360 S429 T467 T133 T269 T292 T323 S339		EF-hand Calcium binding domain: D231- D421	g3297882 atopy-related autoantigen CALC [H. sapiens].	Motifs BLAST_GENBANK HMMER_PFAM BLAST_PRODROM

Table 2 (cont.)

22 (1682320)	171	T70 T151 S97 Y11 Y24		Leucine zipper: L38- L59 Peptidyl-Prolyl Cis- Trans Isomerase CYP6: L59-F170	g1354207 rof1 FK506 binding protein	Motifs BLAST_GENBANK BLAST_PRODOME BLAST_DOMO
23 (1728263)	163	S16 S39 S56 T101 T112 T131 S148 Y92	N70	EF-hand calcium binding domain: D140- F152	g21209 caltractin [Scherffelia dubia]	Motifs BLAST_GENBANK BLAST_PRODOME
24 (1867626)	354	T230 T148 T252 S306 S315 T328 S8 T20 T27 S40 S71 T189 T244 T259 T288	N58 N64 N146 N250	Leucine zipper: L326- L347 ATP-Binding motif: E93-E320 Vasodilator-Stimulated Actin-Binding Phosphoprotein motif: M1-A109	g3834607 homer-1b [Mus musculus]	Motifs BLAST_GENBANK BLAST_PRODOME
25 (1990126)	365	T36 S47 S191 T198 S200 T359 T56 T124 S307 Y80 Y155	N189 N264 N297 N320	Src homology domain 3: R308-L364	g1407657 endophilin II	Motifs BLAST_GENBANK HMMER_PPFAM BLIMPS_PRINTS BLAST_DOMO
26 (2104180)	274	T71 S126 T137 S230 S251 T7 S141 S155 Y152	N56	Protein Kinase C2 domain: L55-H135	g3876326 similar to protein kinase C2	Motifs BLAST_GENBANK HMMER_PPFAM
27 (2122241)	129	T11 S24 S58 T100 S112 T89		Nascent polypeptide- associated complex alpha chain: G39-T128		Motifs BLAST_DOMO
28 (2580428)	626	S84 S93 S192 S278 T411 S10 S18 T114 S302 S482	N293 N577 N599	Interferon-gamma inducible protein motif: M1-M115, C522- A574	g4886493 and g6942315, [H. sapiens].	Motifs BLAST_PRODOME

Table 2 (cont.)

29 (3397189)	157	S7	N97	Signal peptide: M1-S29 Glycosyl hydrolase: L62-L137 Beta D Galactosidase: R28-L153	g2547317 lysosomal beta- galactosidase W09914328	Motifs BLAST_GENBANK SPSCAN HMMER BLIMPS_BLOCKS BLAST_PRODROM
30 (4881249)	383	T7 T26 S90 T62 T81 S102 T363 S3 T210 T256 T286 Y158	N70 N190 N223 N289	WWP (Signal transduction associated proline binding domain): L201- P230	g5059333 ubiquitin ligase	Motifs BLAST_GENBANK HMMER_PFAM BLIMPS_PRINTS
31	478	S186 S202 S270 S354 S455 S9 S94 T175		Signal peptide: M1-A64 Ankyrin repeat: D36-E63 Ankyrin repeat protein domain: Q111-Y174; C285-V447	g1204166 , hypothetical Ank-repeat/BTB- domain protein [Schizosaccharo myces pombe].	MOTIFS SPSCAN HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS BLAST-PRODROM
32	275	S259 T74 T173 S186 T231 S21 T63 T219 S255 S267			COP9 complex subunit 7b [Mus musculus] g3309176	BLAST-Genbank MOTIFS
33	217	T4 T106 S209		Signal peptide: M1-C25 Transmembrane domains: A82-T100; R116-I34 Claudin signature: T21-W30; G49-V55 Q63-L73; D146-V152	claudin-9 protein [Mus musculus] g4325296	BLAST-Genbank MOTIFS SPSCAN HMMER BLIMPS-PRINTS

Table 2 (cont.)

34	74	S6 T58 S54		TPR domain: Y18-P46		MOTIFS HMME-PFAM BLIMPS-PRODUM
35	367	S309 S24	N240	Transmembrane domain: L257-T277 Armadillo/beta-catenin repeat: 219-252; L252-L265		MOTIFS HMME BLIMPS-PFAM
36	1113	T17 S43 S609 T755 T52 T215 S239 S287 T307 T313 S504 S510 S535 T536 S635 S688 S804 S812 T856 S863 T884 S938 T983 S996 S1004 S5 T196 S353 S433 T550 S592 S593 S727 T748 S762 S839 T928 S944 T952 T968 S1074 Y23 Y134	N175 N323 N365 N633 N724	PDZ domains: V53-E135; E152-D237 L252-H335; E472-D560 H573-D657; T673-Q754 K989-N1070 SH3 domain repeat: G98-K111 SH3 domain protein signature: V153-G249 GLGF domain: L676-K752	AMPA receptor interacting protein GRIP [Rattus norvegicus] g1890856	BLAST-Genbank MOTIFS HMME-PFAM BLIMPS-PFAM BLIMPS-PRODUM BLAST-DOMO
37	511	S147 S88 S136 T228 T320 S467 T15 T81 T118 T168 S281 S289 S311 S354 S455 T461 T480 T494 Y16 Y114	N86 N116 N315 N316 N355 N403 N425 N429 N478	SH3 domain: Q342-L400	g6563258, insulin receptor tyrosine kinase substrate [Homo sapiens].	BLAST-Genbank MOTIFS HMME-PFAM

Table 2 (cont.)

38	1177	S421 T936 T96 T121 S164 S209 T256 S277 S325 S374 S388 T397 S435 S443 T456 T519 S662 T669 S727 T901 S983 S1114 S14 T70 S307 S331 S416 S545 T565 S609 T626 T703 S804 S845 S853 S867 T921 S972 T1021 S1108 Y214 Y879 Y171	N84 N1112	Armadillo beta-catenin repeat: I196-L205	trg [Rattus norvegicus] g550420	BLAST-Genbank MOTIFS BLIMPS-PFAM
39	665	S245 T358 S480 T76 S110 S119 S121 T266 S284 S481 S521 S561 S632 S654 S655 S72 S73 S130 T171 S205 T411 S428 T475 S476 T491 S513 S523 T634 Y165 Y567 Y578	N197 N479	TPR domains: L136-P164; Y204-P232 E285-G313; P319-G347 F353-P381 TPR repeat: K137-E252; K286-K395	g6272680, TPR- containing protein involved in spermatogenesis TPIS [Mus musculus]. Takaishi, M. and Huh, N.H. (1999) Biochem. Biophys. Res. Commun. 264:81-85.	BLAST-Genbank MOTIFS HMMER-PFAM BLIMPS-PRODOM BLAST-DOMO
40	125	T119 T67		Signal peptide: M1-A53 SH3 domain: R68-L124 R68-A78; K112-L124		MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS

Table 2 (cont.)

Poly-peptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
41	366	S43 S45 T102 S157 T202 T220 S293 S219 T256 T325 S350 Y237		Signal peptide: M1-S30 Ankyrin repeat: G174-S206	g289693, homology with isopentenyl- diphosphate- delta-isomerase; [C. elegans]. Sulston, J. et al. (1992) Nature 356:37-41.	MOTIFS SPSCAN HMMER-PFAM BLIMPS-PFAM
42	173	S16 S42 S48 T67 S100 S111 S152 S86	N126	EF Hands: E22-R53; L57-F85 K94-M122; L135-L163 S-100/IcaBP type calcium binding protein signature: L6-E57; L132-K168 Recoverin family signature: V61-T82; S86-D105 Calmodulin repeat: R25-I79; L119-S157	calcineurin B- like protein (CBLP) [Rattus norvegicus] g220688	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS PROFILES SCAN BLAST-DOMO
43	761	S227 S293 S393 S19 S43 T149 T161 S277 T346 T370 T415 T529 T572 S630 T683 S711 T746 S74 S196 S252 S283 S300 T444 T472 T591 S754 Y589	N117 N467 N492 N555	3',5'-cyclic nucleotide phosphodiesterase domain: Y490-H729 D418-W744 3',5'-cyclic nucleotide phosphodiesterase signature: L2-H56; L449-H485 Y490- H501; L516-D556 T572-E610; D657-S711	CAMP-specific cyclic nucleotide phosphodiesterase PDE8 [Mus musculus].	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS PROFILES SCAN BLAST-PRODOM BLAST-DOMO

Table 2 (cont.)

Poly-peptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
44	249	S16 S89 T115 S212 S239 T12 T117 S137 S187 S197 S230 Y208	N84	Pleckstrin homology domain: V35-T131 Rho-GEF domain: L36-C178; E118-D245 FYVE zinc finger: N59-Y64; R171-C183 R202-S212	g3292902, PUTATIVE RHO/RAC GUANINE NUCLEOTIDE EXCHANGE FACTOR [H. sapiens].	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-PFAM BLAST-PRODROM
45	247	S109 S44 S53 S123 T138 S167 S95 T98 S127 T220	N90		putative phosphatidyl- inositol 3-kinase [Carassius auratus] g4001815	BLAST-GenBank MOTIFS
46	316	S313 S201 T223 T262 Y186 Y270			g3811347, cytosolic phospholipase A2 beta [Homo sapiens].	BLAST-GenBank MOTIFS
47	334	T119 S97 T182 T244 S316 S317 S324 S60 T72 S97 T179 S187 S290 Y52 Y323	N58 N322	Fes/CIP4 homology domain: G8-L98 SH3 domain/division control protein signature: F6-F287	macrophage actin- associated- tyrosine- phosphorylated protein [Mus musculus] g3947712	BLAST-GenBank MOTIFS HMMER-PFAM BLAST-PRODROM
48	113	T65 S66 T43		SH3 domain: K34-L90	SLP-76 associated protein (TCR- stimulated PK substrate) [Homo sapiens] g2072873	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-PRINTS

Table 2 (cont.)

Poly-peptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
49	264	S18 T76 T163 S181 S167 S223		Wilm's tumor protein signature: D97-P111	SH3 domain binding protein [Rattus norvegicus] g1185397 (P-value= 4.6x10- 8).	BLAST-GenBank MOTIFS BLIMPS-PRINTS
50	185	T24 S81 S149 S151 S160 S162 S75 S99 S177 Y176		EF-hands: K101-L129; L143-S171 Recoverin family signature: I23-G42; S93-N112 Calcium binding protein signature: E12-Y104	g1848271, Calcium and integrin binding protein CIB [Homo sapiens]	BLAST-GenBank MOTIFS HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS BLAST-PRODOM
51	72	T18 S25 T20		Synapse-associated SH3 domain protein signature: M13-E67	homolog of Drosophila discs large protein isoform 1 [Homo sapiens] g558438 (P-value= 7.9x10- 9).	BLAST-GenBank MOTIFS BLAST-PRODOM
52	434	S123 T128 S418 S94 T105 S159 S205 T291 S308 S314 T326 T358 S383 S406 S84 T128 T212 Y220	N216 N231	Signal peptide: M1-A50 EF hand: I366-R394 Recoverin family signature: V370-L391	similar to EF hand [C. elegans] g3875264.	BLAST-GenBank MOTIFS SPSCAN HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS

Table 3

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
53	543-587	Reproductive (0.211) Developmental (0.158) Nervous (0.158)	Cancer (0.421) Cell Proliferation (0.263) Inflammation (0.211)	PBLUESCRIPT
54	273-317 651-695	Nervous (0.462) Gastrointestinal (0.385) Cardiovascular (0.077) Developmental (0.077)	Cancer (0.538) Cell Proliferation (0.308) Inflammation (0.154)	PSPORT1
55	110-154	Developmental (0.174) Gastrointestinal (0.174) Reproductive (0.174)	Cell Proliferation (0.435) Cancer (0.261) Inflammation (0.174)	pINCY
56	273-317 1461-1505	Gastrointestinal (0.821) Reproductive (0.143) Developmental (0.036)	Cancer (0.607) Inflammation (0.286) Cell Proliferation (0.036)	pINCY
57	595-639	Reproductive (0.313) Nervous (0.217) Hematopoietic/Immune (0.120)	Cancer (0.482) Inflammation (0.217) Cell Proliferation (0.169)	pINCY
58	703-747 1297-1341	Reproductive (0.250) Nervous (0.205) Gastrointestinal (0.125)	Cancer (0.509) Cell Proliferation (0.196) Inflammation (0.196)	pINCY
59	417-461	Nervous (0.300) Cardiovascular (0.200) Reproductive (0.200)	Inflammation (0.300) Trauma (0.300) Cancer (0.200) Cell Proliferation (0.200)	pINCY
60	1189-1233	Nervous (1.000)	Neurological (0.500) Trauma (0.333)	PSPORT1
61	272-316	Reproductive (0.314) Gastrointestinal (0.186) Nervous (0.157)	Cancer (0.529) Inflammation (0.200) Cell Proliferation (0.129)	PSPORT1
62	273-317 2055-2099	Hematopoietic/Immune (0.333) Reproductive (0.238) Gastrointestinal (0.167)	Inflammation (0.452) Cancer (0.333) Trauma (0.143)	PSPORT1
63	1-34	Reproductive (0.256) Nervous (0.188) Gastrointestinal (0.120)	Cancer (0.504) Inflammation (0.203) Cell Proliferation (0.195)	PSPORT1

Table 3 (cont.)

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
64	489-533	Reproductive (0.312) Gastrointestinal (0.125) Nervous (0.125)	Cancer (0.438) Cell Proliferation (0.375) Inflammation (0.188)	pINCY
65	273-317	Reproductive (0.265) Nervous (0.224) Developmental (0.102)	Cancer (0.469) Cell Proliferation (0.286) Inflammation (0.204)	pINCY
66	1028-1072	Cardiovascular (0.286) Nervous (0.200) Reproductive (0.200)	Cancer (0.429) Cell Proliferation (0.171) Inflammation (0.171)	pINCY
67	325-369	Reproductive (0.222) Nervous (0.194) Cardiovascular (0.167) Gastrointestinal (0.167)	Cancer (0.472) Cell Proliferation (0.333) Inflammation (0.139)	pINCY
68	921-965	Endocrine (0.250) Musculoskeletal (0.250) Reproductive (0.250) Urologic (0.250)	Cancer (0.750) Trauma (0.250)	pINCY
69	1029-1073	Reproductive (0.216) Gastrointestinal (0.176) Hematopoietic/Immune (0.157)	Cancer (0.510) Inflammation (0.275) Cell Proliferation (0.118)	pINCY
70	1405-1449	Hematopoietic/Immune (0.200) Nervous (0.200) Gastrointestinal (0.160) Reproductive (0.160)	Cancer (0.360) Inflammation (0.360) Cell Proliferation (0.200)	pINCY
71	280-324	Hematopoietic/Immune (0.500) Gastrointestinal (0.092) Reproductive (0.092)	Cancer (0.364) Inflammation (0.295) Cell proliferation (0.205)	pBLUESCRIPT
72	380-424	Reproductive (0.227) Gastrointestinal (0.205) Cardiovascular (0.114)	Cancer (0.455) Inflammation (0.364) Trauma (0.045)	pBLUESCRIPT

Table 3 (cont.)

73	433-477	Nervous (0.241) Reproductive (0.231) Gastrointestinal (0.130)	Cancer (0.398) Inflammation (0.333)	pINCY
74	786-830	Reproductive (0.342) Nervous (0.210)	Cancer (0.474) Cell proliferation (0.184) Inflammation (0.105)	pINCY
75	1-47	Gastrointestinal (0.286) Reproductive (0.286) Developmental (0.143) Hematopoietic/Immune (0.143)	Cancer (0.571) Cell proliferation (0.286) Inflammation (0.143)	pINCY
76	380-424	Nervous (0.300) Reproductive (0.200)	Inflammation (0.400) Cancer (0.200) Cell proliferation (0.200)	pINCY
77	30-74	Gastrointestinal (0.222) Reproductive (0.222) Cardiovascular (0.153) Nervous (0.153)	Inflammation (0.375) Cancer (0.361) Cell proliferation (0.139)	pINCY
78	487-531	Nervous (0.300) Reproductive (0.183) Cardiovascular (0.117)	Cancer (0.433) Inflammation (0.200) Neurological (0.133)	pSPORT1
79	595-639	Reproductive (0.305) Nervous (0.179) Gastrointestinal (0.126)	Cancer (0.526) Inflammation (0.326) Cell proliferation (0.179)	pINCY
80	109-153	Reproductive (0.235) Hematopoietic/Immune (0.216) Nervous (0.157)	Cancer (0.529) Inflammation (0.255)	pINCY
81	109-153	Gastrointestinal (0.286) Musculoskeletal (0.286) Reproductive (0.286)	Cancer (0.571) Inflammation (0.286)	pINCY
82	163-207	Reproductive (0.424) Gastrointestinal (0.152) Nervous (0.121)	Cancer (0.424) Inflammation (0.242) Cell proliferation (0.182)	pINCY
83	496-540	Reproductive (0.242) Nervous (0.182) Hematopoietic/Immune (0.167)	Cancer (0.455) Inflammation/Trauma (0.364) Cell Proliferation (0.152)	pSPORT1
84	1022-1066	Reproductive (0.248) Nervous (0.208) Cardiovascular (0.136)	Cancer (0.464) Inflammation/Trauma (0.304) Cell Proliferation (0.184)	pSPORT1

Table 3 (cont.)

85	39-83	Nervous (0.286) Endocrine (0.143) Gastrointestinal (0.143) Hematopoietic/Immune (0.143) Reproductive (0.143)	Cancer (0.571) Inflammation/Trauma (0.286) Neurological (0.143)	PSPORT1
86	471-515	Hematopoietic/Immune (0.167) Musculoskeletal (0.167) Reproductive (0.167)	Cancer (0.556) Cell Proliferation (0.167) Inflammation/Trauma (0.167)	PSPORT1
87	595-639 982-1026	Reproductive (0.294) Cardiovascular (0.176) Gastrointestinal (0.176)	Cancer (0.706) Inflammation/Trauma (0.294) Cell Proliferation (0.118)	PSPORT1
88	1101-1163	Reproductive (0.625) Gastrointestinal (0.250) Cardiovascular (0.125)	Cancer (0.750) Inflammation/Trauma (0.250)	PSPORT1
89	1245-1289	Gastrointestinal (0.387) Reproductive (0.355) Cardiovascular (0.065)	Cancer (0.548) Inflammation/Trauma (0.323) Cell Proliferation (0.161)	pINCY
90	3720-3764	Nervous (0.328) Gastrointestinal (0.121) Reproductive (0.121)	Cancer (0.397) Inflammation/Trauma (0.310) Cell Proliferation (0.155)	pINCY
91	659-703 1622-1666	Hematopoietic/Immune (0.273) Nervous (0.182) Cardiovascular (0.121) Reproductive (0.121)	Cancer (0.455) Cell Proliferation (0.333) Inflammation/Trauma (0.303)	pINCY
92	104-148	Reproductive (0.310) Nervous (0.241) Developmental (0.138) Gastrointestinal (0.138)	Cancer (0.483) Inflammation/Trauma (0.241) Cell Proliferation (0.172)	pINCY
93	820-864	Reproductive (0.340) Cardiovascular (0.120) Nervous (0.120)	Inflammation/Trauma (0.440) Cancer (0.400) Cell Proliferation (0.160)	pINCY
94	504-554	Reproductive (1.000)	Inflammation/Trauma (1.000)	PBLUESCRIPT
95	198-242	Reproductive (0.424) Nervous (0.273)	Cancer (0.576) Inflammation/Trauma (0.182)	PSPORT1
96	307-351 712-756	Reproductive (0.412) Hematopoietic/Immune (0.137) Cardiovascular (0.118) Gastrointestinal (0.118)	Cancer (0.608) Inflammation/Trauma (0.275) Cell Proliferation (0.098)	pINCY

Table 3 (cont.)

97	433-477	Developmental (0.200) Reproductive (0.200) Cardiovascular (0.133) Gastrointestinal (0.133) Nervous (0.133)	Cell Proliferation (0.400) Cancer (0.333) Inflammation/Trauma (0.200)	pINCY
98	474-1018	Cardiovascular (0.190) Reproductive (0.190) Hematopoietic/Immune (0.143) Musculoskeletal (0.143)	Cancer (0.381) Inflammation/Trauma (0.333)	pINCY
99	422-466 998-1042	Hematopoietic/Immune (0.667) Reproductive (0.222) Developmental (0.111)	Inflammation/Trauma (0.556) Cancer (0.222) Cell Proliferation (0.222)	pINCY
100	444-488	Hematopoietic/Immune (0.455) Nervous (0.182) Cardiovascular (0.091)	Inflammation/Trauma (0.546) Cancer (0.182) Cell Proliferation (0.182)	pINCY
101	1578-1622	Reproductive (0.250) Nervous (0.170) Gastrointestinal (0.156)	Cancer (0.482) Inflammation/Trauma (0.345) Cell Proliferation (0.167)	pINCY
102	15-59	Cardiovascular (1.000)	Cancer (1.000)	pINCY
103	487-531	Hematopoietic/Immune (1.000)		pINCY
104	967-1011	Reproductive (0.235) Nervous (0.191) Gastrointestinal (0.147)	Cancer (0.515) Inflammation/Trauma (0.294) Cell Proliferation (0.118)	pINCY

Table 4

Nucleotide SEQ ID NO:	Library	Library Description
53	TESTNOT01	The library was constructed using RNA isolated from the testicular tissue of a 37-year-old Caucasian male, who died from liver disease. Patient history included cirrhosis, jaundice, and liver failure.
54	COLNNOT05	The library was constructed using RNA isolated from the sigmoid colon tissue of a 40-year-old Caucasian male during a partial colectomy. Pathology indicated Crohn's disease involving the proximal colon and including the cecum. The ascending and transverse colon displayed linear ulcerations and skip lesions. Transmural inflammation was present.
55	KIDNNOT09	The library was constructed using RNA isolated from the kidney tissue of a Caucasian male fetus who died at 23 weeks' gestation.
56	COLNFET02	The library was constructed using RNA isolated from the colon tissue of a Caucasian female fetus who died at 20 weeks' gestation.
57	CONNNOT01	The library was constructed using RNA isolated from mesentery fat tissue obtained from a 71-year-old Caucasian male during a partial colectomy and permanent colostomy. Family history included atherosclerotic coronary artery disease, myocardial infarction, and extrinsic asthma.
58	BRAINNOT09	The library was constructed using RNA isolated from brain tissue removed from a Caucasian male fetus who died at 23 weeks' gestation.
59	ENDCNOT02	The library was constructed using RNA isolated from dermal microvascular endothelial cells removed from a 30-year-old Caucasian female.
60	HIPONON02	This normalized library was constructed using 1.13 million independent clones from a hippocampus library. RNA was isolated from the hippocampus tissue of a 72-year-old Caucasian female who died from an intracranial bleed. Patient history included nose cancer, hypertension, and arthritis. The normalization and hybridization conditions were adapted from Soares et al. (PNAS (1994) 91:9228).
61	OVARNOT02	The library was constructed using RNA isolated from ovarian tissue removed from a 59-year-old Caucasian female who died of a myocardial infarction. Patient history included cardiomyopathy, coronary artery disease, myocardial infarction, hypercholesterolemia, hypotension, and arthritis.
62	OVARNOT02	The library was constructed using RNA isolated from ovarian tissue removed from a 59-year-old Caucasian female who died of a myocardial infarction. Patient history included cardiomyopathy, coronary artery disease, myocardial infarction, hypercholesterolemia, hypotension, and arthritis.

Table 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Description
63	ADRETUT01	The library was constructed using RNA isolated from right adrenal tumor tissue removed from a 50-year-old Turkish male during a unilateral adrenalectomy. Pathology indicated a metastatic renal cell carcinoma that formed a circumscribed, spongy, hemorrhagic nodule situated in the region of the medulla. The patient presented with corticoadrenal insufficiency, incisional hernia, and non-alcoholic steato hepatitis. Patient history included renal cell carcinoma. Family history included liver cancer.
64	GBLANOT01	The library was constructed using RNA isolated from diseased gallbladder tissue removed from a 53-year-old Caucasian female during a cholecystectomy. Pathology indicated mild chronic cholecystitis and cholelithiasis with approximately 150 mixed gallstones. Family history included benign hypertension.
65	LUNGTUT09	The library was constructed using RNA isolated from lung tumor tissue removed from a 68-year-old Caucasian male during segmental lung resection. Pathology indicated invasive grade 3 squamous cell carcinoma and a metastatic tumor. Patient history included type II diabetes, thyroid disorder, depressive disorder, hyperlipidemia, esophageal ulcer, and tobacco use.
66	PONSAZT01	The library was constructed using RNA isolated from diseased pons tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease.
67	293TF1T01	The library was constructed using RNA isolated from a transformed embryonal cell line (293-EBNA) derived from kidney epithelial tissue. The cells were transformed with adenovirus 5 DNA.
68	ADRENOT14	The library was constructed using RNA isolated from adrenal gland tissue removed from an 8-year-old Black male who died from anoxia.
69	BRAVXT03	The library was constructed using RNA isolated from treated astrocytes removed from the brain of a female fetus who died at 22 weeks' gestation. The cells were treated with tumor necrosis factor (TNF) alpha and interleukin 1 (IL-1), 10ng/ml each for 24 hours.

Table 4 (cont.)

70	293TF2T01	The library was constructed using RNA isolated from a treated, transformed embryonal cell line (293-EBNA) derived from kidney epithelial tissue. The cells were treated with 5-aza-2'-deoxycytidine and transformed with adenovirus 5 DNA.
71	THPINOB01	Library was constructed using RNA isolated from cultured, unstimulated THP-1 cells. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia. RNA was isolated from 2x10 ⁸ cells using GuSCN lysis, followed by DNase treatment.
72	TESTNOT01	Library was constructed using RNA isolated from the testicular tissue of a 37-year-old Caucasian male, who died from liver disease. Patient history included cirrhosis, jaundice, and liver failure.
73	LUNGNOT09	Library was constructed using RNA isolated from the lung tissue of a 23-week-old Caucasian male fetus. The pregnancy was terminated following a diagnosis by ultrasound of infantile polycystic kidney disease.
74	PROSNOT15	Library was constructed using RNA isolated from diseased prostate tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 2+3). The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer, secondary bone cancer, and benign hypertension.
75	PROSNOT14	Library was constructed using RNA isolated from diseased prostate tissue removed from a 60-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 3+4). Family history included benign hypertension, cerebrovascular disease, and arteriosclerotic coronary artery disease.
76	SKINBIT01	Library was constructed using RNA isolated from diseased skin tissue of the left lower leg. Patient history included erythema nodosum of the left lower leg.
77	CORPNOT02	Library was constructed using RNA isolated from diseased corpus callosum tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease.
78	BRAITUT02	Library was constructed using RNA isolated from brain tumor tissue removed from the frontal lobe of a 58-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a grade 2 metastatic hypernephroma. Patient history included a grade 2 renal cell carcinoma, insomnia, and chronic airway obstruction. Family history included a malignant neoplasm of the kidney.

Table 4 (cont.)

79	BRSTNOT07	Library was constructed using RNA isolated from diseased breast tissue removed from a 43-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated mildly proliferative fibrocystic changes with epithelial hyperplasia, papillomatosis, and duct ectasia. Pathology for the associated tumor tissue indicated invasive grade 4, nuclear grade 3 mammary adenocarcinoma with extensive comedo necrosis. Family history included epilepsy, cardiovascular disease, and type II diabetes.
80	KIDNTUT13	Library was constructed using RNA isolated from kidney tumor tissue removed from a 51-year-old Caucasian female during a nephroureterectomy. Pathology indicated a grade 3 renal cell carcinoma. Family history included calculus of the kidney, colon cancer, and type II diabetes.
81	UTRSNOT16	Library was constructed using RNA isolated from uterine endometrial tissue removed from a 48-year-old Caucasian female during a vaginal hysterectomy, rectocele repair, and bilateral salpingo-oophorectomy. Pathology indicated chronic cervicitis, and the endometrium was weakly proliferative. Pathology for the associated tumor tissue indicated a single submucosal leiomyoma. Patient history included hyperlipidemia and meningitis. Family history included benign hypertension, hyperlipidemia, atrial fibrillation, atherosclerotic coronary artery disease, and type II diabetes.
82	UTRWTTMT01	Library was constructed using RNA isolated from myometrial tissue removed from a 45-year-old Caucasian female during vaginal hysterectomy and bilateral salpingo-oophorectomy. Pathology indicated the myometrium was negative for tumor. Pathology for the associated tumor tissue indicated multiple (23) subserosal, intramural, and submucosal leiomyomata. Patient history included extrinsic asthma without status asthmaticus and normal delivery. Family history included cerebrovascular disease, depression, and atherosclerotic coronary artery disease. This library was constructed using RNA isolated from pooled diseased eosinophils obtained from allergic asthmatic individuals.
83	EOSINOT03	This library was constructed using RNA isolated from pooled eosinophils obtained from allergic asthmatic individuals.
84	EOSINOT02	This library was constructed using RNA isolated from the cerebellum tissue of a 69-year-old Caucasian male who died from chronic obstructive pulmonary disease. Patient history included myocardial infarction, hypertension, and osteoarthritis.
85	CRBLNOT01	This library was constructed using RNA isolated from the knee synovial membrane tissue of an 82-year-old female with osteoarthritis.
86	SYNOOAT01	This library was constructed using RNA isolated from diseased breast tissue removed from a 54-year-old Caucasian female during a bilateral radical mastectomy. Pathology for the associated tumor tissue indicated residual invasive grade 3 mammary ductal adenocarcinoma. Patient history included kidney infection and condyloma acuminatum.
87	BRSTNOT03	

		Family history included benign hypertension, hyperlipidemia, and a malignant neoplasm of the colon.
88	LUNGNOT03	This library was constructed using RNA isolated from lung tissue of a 79-year-old Caucasian male. Pathology for the associated tumor tissue indicated grade 4 carcinoma. Patient history included a benign prostate neoplasm and atherosclerosis.
89	COLNNOT13	This library was constructed using RNA isolated from ascending colon tissue of a 28-year-old Caucasian male with moderate chronic ulcerative colitis.
90	LARTUT02	This library was constructed using RNA isolated from a myxoma removed from the left atrium of a 43-year-old Caucasian male during annuloplasty. Pathology indicated atrial myxoma. Patient history included pulmonary insufficiency, acute myocardial infarction, atherosclerotic coronary artery disease, hyperlipidemia, and tobacco use. Family history included benign hypertension, acute myocardial infarction, atherosclerotic coronary artery disease, and type II diabetes.
91	PROSNOT15	This library was constructed using RNA isolated from diseased prostate tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 2+3). The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer, secondary bone cancer, and benign hypertension.
92	PROSTUT10	This library was constructed using RNA isolated from prostatic tumor tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated an adenocarcinoma (Gleason grade 2+3). Adenofibromatous hyperplasia was also present. The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer and secondary bone cancer.
93	PROSTUT12	This library was constructed using RNA isolated from prostate tumor tissue removed from a 65-year-old Caucasian male during a radical prostatectomy. Pathology indicated an adenocarcinoma (Gleason grade 2+2). Adenofibromatous hyperplasia was also present. The patient presented with elevated prostate specific antigen (PSA).
94	TESTNOT03	This library was constructed using RNA isolated from testicular tissue removed from a 37-year-old Caucasian male, who died from liver disease. Patient history included cirrhosis, jaundice, and liver failure.
95	BRAINON01	This library was constructed and normalized from 4.88 million independent clones from a brain library. RNA was made from brain tissue removed from a 26-year-old Caucasian male during cranioplasty and excision of a cerebral meningeal lesion. Pathology for the associated tumor tissue indicated a grade 4 oligoastrocytoma in the right fronto-parietal part of the brain.

Table 4 (cont.)

96	ISLTNOT01	This library was constructed using RNA isolated from a pooled collection of pancreatic islet cells.
97	COLNTUT16	This library was constructed using RNA isolated from colon tumor tissue obtained from a 60-year-old Caucasian male during a left hemicolectomy. Pathology indicated an invasive grade 2 adenocarcinoma, forming a sessile mass. Patient history included thrombophlebitis, inflammatory polyarthropathy, prostatic inflammatory disease, and depressive disorder. Previous surgeries included resection of the rectum. Family history included atherosclerotic coronary artery disease and colon cancer.
98	THYRNOT10	This library was constructed using RNA isolated from the diseased left thyroid tissue removed from a 30-year-old Caucasian female during a unilateral thyroid lobectomy and parathyroid reimplantation. Pathology indicated lymphocytic thyroiditis.
99	PROSBPT03	This library was constructed using RNA isolated from diseased prostate tissue removed from a 59-year-old Caucasian male during a radical prostatectomy and regional lymph node excision. Pathology indicated benign prostatic hyperplasia (BPH). Pathology for the associated tumor indicated benign adenocarcinoma, Gleason grade 3+3. The patient presented with elevated prostate specific antigen (PSA), benign hypertension, and hyperlipidemia. Family history included cerebrovascular disease, benign hypertension and prostate cancer.
100	BMARNOT03	This library was constructed using RNA isolated from the left tibial bone marrow tissue of a 16-year-old Caucasian male during a partial left tibial osteotomy with free skin graft. Patient history included an abnormality of the red blood cells. Family history included osteoarthritis.
101	UTRSNOT05	This library was constructed using RNA isolated from the uterine tissue of a 45-year-old Caucasian female during a total abdominal hysterectomy and total colectomy. Pathology for the associated tumor tissue indicated multiple leiomyomas of the myometrium and a grade 2 colonic adenocarcinoma of the cecum. Patient history included multiple sclerosis and mitral valve disorder. Family history included type I diabetes, cerebrovascular disease, atherosclerotic coronary artery disease, malignant skin neoplasm, hypertension, and malignant neoplasm of the colon.

Table 4 (cont.)

102	LUNGNOT35	This library was constructed using RNA isolated from lung tissue removed from a 62-year-old Caucasian female. Pathology for the associated tumor tissue indicated a grade 1 spindle cell carcinoid forming a nodule. Patient history included depression, thrombophlebitis, and hyperlipidemia. Family history included cerebrovascular disease, atherosclerotic coronary artery disease, breast cancer, colon cancer, type II diabetes, and malignant skin melanoma.
103	THYMNOT11	This library was constructed using RNA isolated from thymus tissue removed from a 2-year-old Caucasian female during a thymectomy and patch closure of left atrioventricular fistula. The patient presented with congenital heart abnormalities. Patient history included double inlet left ventricle and a rudimentary right ventricle, pulmonary hypertension, cyanosis, subaortic stenosis, seizures, and a fracture of the skull base. Family history included reflux neuropathy.
104	KIDNNOT34	This library was constructed using RNA isolated from left kidney tissue obtained from an 8-year-old Caucasian male who died from an intracranial hemorrhage.

Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises at least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad. Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	ESTs: fasta E value=1.06E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less Full Length sequences: fastx score=100 or greater
BLIMPS	A BLOCKS IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and, if applicable, Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

Table 5 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribkov, M. et al. (1988) CABIOS 4:61-66; Gribkov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Normalized quality score>GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=3.5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. <u>supra</u> ; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

5 a) an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID
NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8,
SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14,
SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20,
SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26,
10 SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34,
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SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46,
SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID
NO:52.

b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52,

25 c) a biologically active fragment of an amino acid sequence selected from the group
consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID
NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12,
SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18,
SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24,
30 SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30,
SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38,
SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44,
SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50;
SEQ ID NO:51, and SEQ ID NO:52, and

d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52.

2. An isolated polypeptide of claim 1 selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52.

3. An isolated polynucleotide encoding a polypeptide of claim 1.

4. An isolated polynucleotide encoding a polypeptide of claim 2.

5. An isolated polynucleotide of claim 4 selected from the group consisting of SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID

NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, and SEQ ID NO:104.

5 6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.

7. A cell transformed with a recombinant polynucleotide of claim 6.

10 8. A transgenic organism comprising a recombinant polynucleotide of claim 6.

9. A method for producing a polypeptide of claim 1, the method comprising:

15 a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1, and

b) recovering the polypeptide so expressed.

10. An isolated antibody which specifically binds to a polypeptide of claim 1.

20 11. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:

a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104,

b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:53-104,

25 c) a polynucleotide sequence complementary to a),

d) a polynucleotide sequence complementary to b), and

e) an RNA equivalent of a)-d).

30 12. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 11.

13. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

35 a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe

specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and

b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

5

14. A method of claim 13, wherein the probe comprises at least 60 contiguous nucleotides.

15. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

10 a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and

b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

15 16. A pharmaceutical composition comprising an effective amount of a polypeptide of claim 1 and a pharmaceutically acceptable excipient.

17. A pharmaceutical composition of claim 16, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52.

18. A method for treating a disease or condition associated with decreased expression of functional INTRA, comprising administering to a patient in need of such treatment the pharmaceutical composition of claim 16.

19. A method for screening a compound for effectiveness as an agonist of a polypeptide of claim 1, the method comprising:

35 a) exposing a sample comprising a polypeptide of claim 1 to a compound, and

b) detecting agonist activity in the sample.

20. A pharmaceutical composition comprising an agonist compound identified by a method of claim 19 and a pharmaceutically acceptable excipient.

5

21. A method for treating a disease or condition associated with decreased expression of functional INTRA, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 20.

10 22. A method for screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting antagonist activity in the sample.

15 23. A pharmaceutical composition comprising an antagonist compound identified by a method of claim 22 and a pharmaceutically acceptable excipient.

20 24. A method for treating a disease or condition associated with overexpression of functional INTRA, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 23.

25 25. A method of screening for a compound that specifically binds to the polypeptide of claim 1, said method comprising the steps of:

- a) combining the polypeptide of claim 1 with at least one test compound under suitable conditions, and
- b) detecting binding of the polypeptide of claim 1 to the test compound, thereby identifying a compound that specifically binds to the polypeptide of claim 1.

30 26. A method of screening for a compound that modulates the activity of the polypeptide of claim 1, said method comprising:

- a) combining the polypeptide of claim 1 with at least one test compound under conditions permissive for the activity of the polypeptide of claim 1,
- b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound, and

c) comparing the activity of the polypeptide of claim 1 in the presence of the test compound with the activity of the polypeptide of claim 1 in the absence of the test compound, wherein a change in the activity of the polypeptide of claim 1 in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide of claim 1.

5

27. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 5, the method comprising:

- a) exposing a sample comprising the target polynucleotide to a compound, and
- b) detecting altered expression of the target polynucleotide.

10

SEQUENCE LISTING

<110> INCYTE GENOMICS, INC.
 YUE, Henry
 TANG, Y. Tom
 HILLMAN, Jennifer L.
 LAL, Preeti
 BANDMAN, Olga
 BAUGHN, Mariah R.
 AZIMZAI, Yalda
 YANG, Junming
 REDDY, Roopa
 LU, Dyung Aina M.

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His Leu Lys Phe	Ala Arg Thr Arg Glu	Asn Gln Val Val Leu	Gly		
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Gln His Ser Gly	Pro Phe Pro Ser Val	Pro Glu Leu Val Leu	His		
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1				5					10					15
Tyr	Ser	Gln	Asn	Leu	Thr	Ser	Glu	Pro	Thr	Leu	Leu	Gln	His	Arg
				20					25					30
Val	Glu	His	Leu	Met	Thr	Cys	Lys	Gln	Gly	Ser	Gln	Arg	Val	Gln
				35					40					45
Gly	Pro	Glu	Asp	Ala	Leu	Gln	Lys	Leu	Phe	Glu	Met	Asp	Ala	Gln
				50					55					60
Gly	Arg	Val	Trp	Ser	Gln	Asp	Leu	Ile	Leu	Gln	Val	Arg	Asp	Gly
				65					70					75
Trp	Leu	Gln	Leu	Leu	Asp	Ile	Glu	Thr	Lys	Glu	Glu	Leu	Asp	Ser
				80					85					90
Tyr	Arg	Leu	Asp	Ser	Ile	Gln	Ala	Met	Asn	Val	Ala	Leu	Asn	Thr
				95					100					105
Cys	Ser	Tyr	Asn	Ser	Ile	Leu	Ser	Ile	Thr	Val	Gln	Glu	Pro	Gly
				110					115					120
Leu	Pro	Gly	Thr	Ser	Thr	Leu	Leu	Phe	Gln	Cys	Gln	Glu	Val	Gly
				125					130					135
Ala	Glu	Arg	Leu	Lys	Thr	Ser	Leu	Gln	Lys	Ala	Leu	Glu	Glu	Glu
				140					145					150
Leu	Glu	Gln	Arg	Pro	Arg	Leu	Gly	Gly	Leu	Gln	Pro	Ser	Gln	Asp
				155					160					165
Arg	Trp	Arg	Gly	Pro	Ala	Met	Glu	Arg	Pro	Leu	Pro	Met	Glu	Gln
				170					175					180
Ala	Arg	Tyr	Leu	Glu	Pro	Gly	Ile	Pro	Pro	Glu	Gln	Pro	His	Gln
				185					190					195
Arg	Thr	Leu	Glu	His	Ser	Leu	Pro	Pro	Ser	Pro	Arg	Pro	Leu	Pro
				200					205					210
Arg	His	Thr	Ser	Ala	Arg	Glu	Pro	Ser	Ala	Phe	Thr	Leu	Pro	Pro
				215					220					225
Pro	Arg	Arg	Ser	Ser	Ser	Pro	Glu	Asp	Pro	Glu	Arg	Asp	Glu	Glu
				230					235					240
Val	Leu	Asn	His	Val	Leu	Arg	Asp	Ile	Glu	Leu	Phe	Met	Gly	Lys
				245					250					255
Leu	Glu	Lys	Ala	Gln	Ala	Lys	Thr	Ser	Arg	Lys	Lys	Lys	Phe	Gly
				260					265					270
Lys	Lys	Asn	Lys	Asp	Gln	Gly	Gly	Leu	Thr	Gln	Ala	Gln	Tyr	Ile
				275					280					285
Asp	Cys	Phe	Gln	Lys	Ile	Lys	Tyr	Ser	Phe	Asn	Leu	Leu	Gly	Arg
				290					295					300
Leu	Ala	Thr	Trp	Leu	Lys	Glu	Thr	Ser	Ala	Pro	Glu	Leu	Val	His
				305					310					315
Ile	Leu	Phe	Lys	Ser	Leu	Asn	Phe	Ile	Leu	Ala	Arg	Cys	Pro	Glu
				320					325					330
Ala	Gly	Leu	Ala	Ala	Gln	Val	Ile	Ser	Pro	Leu	Leu	Thr	Pro	Lys

Ala Ile Asn Leu	335	Leu Gln Ser Cys Leu	340	Pro Pro Glu Ser	345
Leu Trp Met Gly	350	Leu Gly Pro Ala Trp	355	Thr Ser Arg Ala	360
Trp Thr Gly Asp	365	Glu Pro Leu Pro Tyr	370	Gln Pro Thr Phe Ser	375
Asp Trp Gln Leu	380	Pro Glu Pro Ser Ser	385	Gln Ala Pro Leu Gly	390
Gln Asp Pro Val	395	Ser Leu Arg Arg Gly	400	Ser His Arg Leu Gly	405
Thr Ser His Phe	410	Pro Gln Glu Lys Thr	415	His Asn His Asp Pro	420
Pro Gly Asp Pro	425	Asn Ser Arg Pro Ser	430	Ser Pro Lys Pro Ala	435
Pro Ala Leu Lys	440	Met Gln Val Leu Tyr	445	Glu Phe Glu Ala Arg	450
Pro Arg Glu Leu	455	Thr Val Val Gln Gly	460	Glu Lys Leu Glu Val	465
Asp His Ser Lys	470	Arg Trp Trp Leu Val	475	Lys Asn Glu Ala Gly	480
Ser Gly Tyr Ile	485	Pro Ser Asn Ile Leu	490	Glu Pro Leu Gln Pro	495
Thr Pro Gly Thr	500	Gln Gly Gln Ser Pro	505	Ser Arg Val Pro Met	510
Arg Leu Ser Ser	515	Arg Pro Glu Glu Val	520	Thr Asp Trp Leu Gln	525
Glu Asn Phe Ser	530	Thr Ala Thr Val Arg	535	Thr Leu Gly Ser Leu	540
Gly Ser Gln Leu	545	Leu Arg Ile Arg Pro	550	Glu Leu Gln Met Leu	555
Cys Pro Gln Glu	560	Ala Pro Arg Ile Leu	565	Ser Arg Leu Glu Ala	570
Arg Arg Met Leu	575	Gly Ile Ser Pro	580		585
	590				

<210> 5

<211> 358

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2020010CD1

<400> 5

Met Ala Gly Pro Gly	5	Pro Thr Phe Pro Leu	10	His Arg Leu Val Trp	15
Ala Asn Arg His Arg	20	Glu Leu Glu Ala Ala	25	Leu His Ser His Gln	30
His Asp Ile Glu Gln	35	Glu Asp Pro Arg Gly	40	Arg Thr Pro Leu Glu	45
Leu Ala Val Ser Leu	50	Gly Asn Leu Glu Ser	55	Val Arg Val Leu Leu	60
Arg His Asn Ala Asn	65	Val Gly Lys Glu Asn	70	Arg Gln Gly Trp Ala	75
Val Leu Gln Glu Ala	80	Val Ser Thr Gly Asp	85	Pro Glu Met Val Gln	90
Leu Val Leu Gln Tyr	95	Arg Asp Tyr Gln Arg	100	Ala Thr Gln Arg Leu	105
Ala Gly Ile Pro Glu	110	Leu Leu Asn Lys Leu	115	Arg Gln Ala Pro Asp	120
Phe Tyr Val Glu Met	125	Lys Trp Glu Phe Thr	130	Ser Trp Val Pro Leu	135
Val Ser Lys Met Cys	140	Pro Ser Asp Val Tyr	145	Arg Val Trp Lys Arg	150
Gly Glu Ser Leu Arg	155	Val Asp Thr Ser Leu	160	Leu Leu Gly Phe Glu	165

Met	Thr	Trp	Gln	Arg	Gly	Arg	Arg	Ser	Phe	Ile	Phe	Lys	Gly	Gln
				170					175					180
Glu	Ala	Gly	Ala	Leu	Val	Met	Glu	Val	Asp	His	Asp	Arg	Gln	Val
				185					190					195
Val	His	Val	Glu	Thr	Leu	Gly	Leu	Thr	Leu	Gln	Glu	Pro	Glu	Thr
				200					205					210
Leu	Leu	Ala	Ala	Met	Arg	Pro	Ser	Glu	Glu	His	Val	Ala	Ser	Arg
				215					220					225
Leu	Thr	Ser	Pro	Ile	Val	Ser	Thr	His	Leu	Asp	Thr	Arg	Asn	Val
				230					235					240
Ala	Phe	Glu	Arg	Asn	Lys	Cys	Gly	Ile	Trp	Gly	Trp	Arg	Ser	Glu
				245					250					255
Lys	Met	Glu	Thr	Val	Ser	Gly	Tyr	Glu	Ala	Lys	Val	Tyr	Ser	Ala
				260					265					270
Thr	Asn	Val	Glu	Leu	Val	Thr	Arg	Thr	Arg	Thr	Glu	His	Leu	Ser
				275					280					285
Asp	Gln	Asp	Lys	Ser	Arg	Ser	Lys	Ala	Gly	Lys	Thr	Pro	Phe	Gln
				290					295					300
Ser	Phe	Leu	Gly	Met	Ala	Gln	Gln	His	Ser	Ser	His	Thr	Gly	Ala
				305					310					315
Pro	Val	Gln	Gln	Ala	Ala	Ser	Pro	Thr	Asn	Pro	Thr	Ala	Ile	Ser
				320					325					330
Pro	Glu	Glu	Tyr	Phe	Asp	Pro	Asn	Phe	Ser	Leu	Glu	Ser	Arg	Asn
				335					340					345
Ile	Gly	Arg	Pro	Ile	Glu	Met	Ser	Ser	Lys	Val	Gln	Arg		
				350					355					

<210> 6

<211> 749

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2149037CD1

<400> 6

Met	Ser	Gly	Ser	His	Thr	Pro	Ala	Cys	Gly	Pro	Phe	Ser	Ala	Leu
1				5					10					15
Thr	Pro	Ser	Ile	Trp	Pro	Gln	Glu	Ile	Leu	Ala	Lys	Tyr	Thr	Gln
				20					25					30
Lys	Glu	Glu	Ser	Ala	Glu	Gln	Pro	Glu	Phe	Tyr	Tyr	Asp	Glu	Phe
				35					40					45
Gly	Phe	Arg	Val	Tyr	Lys	Glu	Glu	Gly	Asp	Glu	Pro	Gly	Ser	Ser
				50					55					60
Leu	Leu	Ala	Asn	Ser	Pro	Leu	Met	Glu	Asp	Ala	Pro	Gln	Arg	Leu
				65					70					75
Arg	Trp	Gln	Ala	His	Leu	Glu	Phe	Thr	His	Asn	His	Asp	Val	Gly
				80					85					90
Asp	Leu	Thr	Trp	Asp	Lys	Ile	Ala	Val	Ser	Leu	Pro	Arg	Ser	Glu
				95					100					105
Lys	Leu	Arg	Ser	Leu	Val	Leu	Ala	Gly	Ile	Pro	His	Gly	Met	Arg
				110					115					120
Pro	Gln	Leu	Trp	Met	Arg	Leu	Ser	Gly	Ala	Leu	Gln	Lys	Lys	Arg
				125					130					135
Asn	Ser	Glu	Leu	Ser	Tyr	Arg	Glu	Ile	Val	Lys	Asn	Ser	Ser	Asn
				140					145					150
Asp	Glu	Thr	Ile	Ala	Ala	Lys	Gln	Ile	Glu	Lys	Asp	Leu	Leu	Arg
				155					160					165
Thr	Met	Pro	Ser	Asn	Ala	Cys	Phe	Ala	Ser	Met	Gly	Ser	Ile	Gly
				170					175					180
Val	Pro	Arg	Leu	Arg	Arg	Val	Leu	Arg	Ala	Leu	Ala	Trp	Leu	Tyr
				185					190					195
Pro	Glu	Ile	Gly	Tyr	Cys	Gln	Gly	Thr	Gly	Met	Val	Ala	Ala	Cys
				200					205					210
Leu	Leu	Leu	Phe	Leu	Glu	Glu	Glu	Asp	Ala	Phe	Trp	Met	Met	Ser
				215					220					225
Ala	Ile	Ile	Glu	Asp	Leu	Leu	Pro	Ala	Ser	Tyr	Phe	Ser	Thr	Thr

Leu Leu Gly Val	230	Thr Asp Gln Arg	235	Val Leu Arg His Leu	240
	245		250		255
Val Gln Tyr Leu	260	Arg Leu Asp Lys	265	Leu Gln Glu His	270
Ile Glu Leu Ser	275	Ile Thr Leu His	280	Phe Leu Thr Ala	285
Ala Ser Val Val	290	Ile Lys Leu Leu	295	Arg Ile Trp Asp	300
Phe Phe Tyr Glu	305	Ser Arg Val Leu	310	Phe Gln Leu Thr	315
Met Leu His Leu	320	Glu Glu Glu Leu	325	Ile Gln Ser Glu Asn	330
Ala Ser Ile Phe	335	Asn Thr Leu Ser Asp	340	Ile Pro Ser Gln Met	345
Asp Ala Glu Leu	350	Leu Leu Gly Val Ala	355	Met Arg Leu Ala Gly	360
Leu Thr Asp Val	365	Val Glu Thr Gln	370	Arg Arg Lys His Leu	375
Tyr Leu Ile Ala	380	Asp Gln Gly Gln Leu	385	Leu Gly Ala Gly Thr	390
Thr Asn Leu Ser	395	Gln Val Val Arg Arg	400	Thr Gln Arg Arg	405
Ser Thr Ile Thr	410	Ala Leu Leu Phe Gly	415	Glu Asp Asp Leu Glu	420
Leu Lys Ala Lys	425	Asn Ile Lys Gln Thr	430	Glu Leu Val Ala Asp	435
Arg Glu Ala Ile	440	Leu Arg Val Ala Arg	445	His Phe Gln Cys Thr	450
Pro Lys Asn Cys	455	Ser Val Glu Leu Thr	460	Pro Asp Tyr Ser Met	465
Ser His Gln Arg	470	Asp His Glu Asn Tyr	475	Val Ala Cys Ser Arg	480
His Arg Arg Arg	485	Ala Lys Ala Leu Leu	490	Asp Phe Glu Arg His	495
Asp Asp Glu Leu	500	Gly Phe Arg Lys Asn	505	Asp Ile Ile Thr Ile	510
Ser Gln Lys Asp	515	Glu His Cys Trp Val	520	Gly Glu Leu Asn Gly	525
Arg Gly Trp Phe	530	Pro Ala Lys Phe Val	535	Glu Val Leu Asp Glu	540
Ser Lys Glu Tyr	545	Ser Ile Ala Gly Asp	550	Asp Ser Val Thr Glu	555
Val Thr Asp Leu	560	Val Arg Gly Thr Leu	565	Cys Pro Ala Leu Lys	570
Leu Phe Glu His	575	Gly Leu Lys Lys Pro	580	Ser Leu Leu Gly Gly	585
Cys His Pro Trp	590	Leu Phe Ile Glu Glu	595	Ala Ala Gly Arg Glu	600
Glu Arg Asp Phe	605	Ala Ser Val Tyr Ser	610	Arg Leu Val Leu Cys	615
Thr Phe Arg Leu	620	Asp Glu Asp Gly Lys	625	Val Leu Thr Pro Glu	630
Leu Leu Tyr Arg	635	Ala Val Gln Ser Val	640	Asn Val Thr His Asp	645
Val His Ala Gln	650	Met Asp Val Lys Leu	655	Arg Ser Leu Ile Cys	660
Gly Leu Asn Glu	665	Gln Val Leu His Leu	670	Trp Leu Glu Val Leu	675
Ser Ser Leu Pro	680	Thr Val Glu Lys Trp	685	Tyr Gln Pro Trp Ser	690
Leu Arg Ser Pro	695	Gly Trp Val Gln Ile	700	Lys Cys Glu Leu Arg	705
Leu Cys Cys Phe	710	Ala Phe Ser Leu Ser	715	Gln Asp Trp Glu Leu	720
Ala Lys Arg Glu	725	Ala Gln Gln Pro Leu	730	Lys Glu Gly Val Arg	735

Met Leu Val Lys His His Leu Phe Ser Trp Asp Val Asp Gly
740 745

<210> 7
<211> 139
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2162179CD1

<400> 7
Met Ala Asp Glu Lys Asp Arg Glu Glu Ile Ile Val Ala Glu Phe
1 5 10 15
His Lys Lys Ile Lys Glu Ala Phe Glu Val Phe Asp His Glu Ser
20 25 30
Asn Asn Thr Val Asp Val Arg Glu Ile Gly Thr Ile Ile Arg Ser
35 40 45
Leu Gly Cys Cys Pro Thr Glu Gly Glu Leu His Asp Leu Ile Ala
50 55 60
Glu Val Glu Glu Glu Glu Pro Thr Gly Tyr Ile Arg Phe Glu Lys
65 70 75
Phe Leu Pro Val Met Thr Glu Ile Leu Leu Glu Arg Lys Tyr Arg
80 85 90
Pro Ile Pro Glu Asp Val Leu Leu Arg Ala Phe Glu Val Leu Asp
95 100 105
Ser Ala Lys Arg Gly Phe Leu Thr Lys Asp Glu Leu Ile Lys Tyr
110 115 120
Met Thr Glu Glu Gly Lys Cys Asp Leu Leu Leu Ile Thr Met Thr
125 130 135
Tyr Val Arg Asn

<210> 8
<211> 539
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2244706CD1

<400> 8
Met Val Gly Lys Pro Val His Lys Gly Ser Glu Ser Pro Asn Ser
1 5 10 15
Phe Leu Asp Gln Glu Tyr Arg Lys Arg Phe Asn Ile Val Glu Glu
20 25 30
Asp Thr Val Leu Tyr Cys Tyr Glu Tyr Glu Lys Gly Arg Ser Ser
35 40 45
Ser Gln Gly Arg Arg Glu Ser Thr Pro Thr Tyr Gly Lys Leu Arg
50 55 60
Pro Ile Ser Met Pro Val Glu Tyr Asn Trp Val Gly Asp Tyr Glu
65 70 75
Asp Pro Asn Lys Met Lys Arg Asp Ser Arg Arg Glu Asn Ser Leu
80 85 90
Leu Arg Tyr Met Ser Asn Glu Lys Ile Ala Gln Glu Glu Tyr Met
95 100 105
Phe Gln Arg Asn Ser Lys Lys Asp Thr Gly Lys Lys Ser Lys Lys
110 115 120
Lys Gly Asp Lys Ser Asn Ser Pro Thr His Tyr Ser Leu Leu Pro
125 130 135
Ser Leu Gln Met Asp Ala Leu Arg Gln Asp Ile Met Gly Thr Pro
140 145 150
Val Pro Glu Thr Thr Leu Tyr His Thr Phe Gln Gln Ser Ser Leu
155 160 165
Gln His Lys Ser Lys Lys Lys Asn Lys Gly Pro Ile Ala Gly Lys
170 175 180
Ser Lys Arg Arg Ile Ser Cys Lys Asp Leu Gly Arg Gly Asp Cys

				185					190					195
Glu	Gly	Trp	Leu	Trp	Lys	Lys	Lys	Asp	Ala	Lys	Ser	Tyr	Phe	Ser
				200					205					210
Gln	Lys	Trp	Lys	Lys	Tyr	Trp	Phe	Val	Leu	Lys	Asp	Ala	Ser	Leu
				215					220					225
Tyr	Trp	Tyr	Ile	Asn	Glu	Glu	Asp	Glu	Lys	Ala	Glu	Gly	Phe	Ile
				230					235					240
Ser	Leu	Pro	Glu	Phe	Lys	Ile	Asp	Arg	Ala	Ser	Glu	Cys	Arg	Lys
				245					250					255
Lys	Tyr	Ala	Phe	Lys	Ala	Cys	His	Pro	Lys	Ile	Lys	Ser	Phe	Tyr
				260					265					270
Phe	Ala	Ala	Glu	His	Leu	Asp	Asp	Met	Asn	Arg	Trp	Leu	Asn	Arg
				275					280					285
Ile	Asn	Met	Leu	Thr	Ala	Gly	Tyr	Ala	Glu	Arg	Glu	Arg	Ile	Lys
				290					295					300
Gln	Glu	Gln	Asp	Tyr	Trp	Ser	Glu	Ser	Asp	Lys	Glu	Glu	Ala	Asp
				305					310					315
Thr	Pro	Ser	Thr	Pro	Lys	Gln	Asp	Ser	Pro	Pro	Pro	Pro	Tyr	Asp
				320					325					330
Thr	Tyr	Pro	Arg	Pro	Pro	Ser	Met	Ser	Cys	Ala	Ser	Pro	Tyr	Val
				335					340					345
Glu	Ala	Lys	His	Ser	Arg	Leu	Ser	Ser	Thr	Glu	Thr	Ser	Gln	Ser
				350					355					360
Gln	Ser	Ser	His	Glu	Glu	Phe	Arg	Gln	Glu	Val	Thr	Gly	Ser	Ser
				365					370					375
Ala	Val	Ser	Pro	Ile	Arg	Lys	Thr	Ala	Ser	Gln	Arg	Arg	Ser	Trp
				380					385					390
Gln	Asp	Leu	Ile	Glu	Thr	Pro	Leu	Thr	Ser	Ser	Gly	Leu	His	Tyr
				395					400					405
Leu	Gln	Thr	Leu	Pro	Leu	Glu	Asp	Ser	Val	Phe	Ser	Asp	Ser	Ala
				410					415					420
Ala	Ile	Ser	Pro	Glu	His	Arg	Arg	Gln	Ser	Thr	Leu	Pro	Thr	Gln
				425					430					435
Lys	Cys	His	Leu	Gln	Asp	His	Tyr	Gly	Pro	Tyr	Pro	Leu	Ala	Glu
				440					445					450
Ser	Glu	Met	Met	Gln	Val	Leu	Asn	Gly	Asn	Gly	Gly	Lys	Pro	Arg
				455					460					465
Arg	Phe	Thr	Leu	Pro	Arg	Asp	Ser	Gly	Phe	Asn	His	Cys	Cys	Leu
				470					475					480
Asn	Ala	Pro	Val	Ser	Ala	Cys	Asp	Pro	Gln	Asp	Asp	Val	Gln	Pro
				485					490					495
Pro	Glu	Val	Glu	Glu	Glu	Glu	Asp	Asp	Glu	Glu	Glu	Ala	Trp	Glu
				500					505					510
Ala	Ala	Gly	Gly	Asn	Met	Gly	Glu	Lys	Ser	Leu	Phe	Thr	Ala	Arg
				515					520					525
Val	Gly	Arg	Pro	Phe	Met	Gln	Asn	Gly	Ser	Thr	Leu	Trp	His	
				530					535					

<210> 9

<211> 319

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2316805CD1

<400> 9

Met	Asp	Pro	Gln	Asn	Gln	His	Gly	Ser	Gly	Ser	Ser	Leu	Val	Val
1				5					10					15
Ile	Gln	Gln	Pro	Ser	Leu	Asp	Ser	Arg	Gln	Arg	Leu	Asp	Tyr	Glu
				20					25					30
Arg	Glu	Ile	Gln	Pro	Thr	Ala	Ile	Leu	Ser	Leu	Asp	Gln	Ile	Lys
				35					40					45
Ala	Ile	Arg	Gly	Ser	Asn	Glu	Tyr	Thr	Glu	Gly	Pro	Ser	Val	Val
				50					55					60
Lys	Arg	Pro	Ala	Pro	Arg	Thr	Ala	Pro	Arg	Gln	Glu	Lys	His	Glu
				65					70					75

Arg	Thr	His	Glu	Ile	Ile	Pro	Ile	Asn	Val	Asn	Asn	Asn	Tyr	Glu	
				80					85					90	
His	Arg	His	Thr	Ser	His	Leu	Gly	His	Ala	Val	Leu	Pro	Ser	Asn	
				95					100					105	
Ala	Arg	Gly	Pro	Ile	Leu	Ser	Arg	Ser	Thr	Ser	Thr	Gly	Ser	Ala	
				110					115					120	
Ala	Ser	Ser	Gly	Ser	Asn	Ser	Ser	Ala	Ser	Ser	Glu	Gln	Gly	Leu	
				125					130					135	
Leu	Gly	Arg	Ser	Pro	Pro	Thr	Arg	Pro	Val	Pro	Gly	His	Arg	Ser	
				140					145					150	
Glu	Arg	Ala	Ile	Arg	Thr	Gln	Pro	Lys	Gln	Leu	Ile	Val	Asp	Asp	
				155					160					165	
Leu	Lys	Gly	Ser	Leu	Lys	Glu	Asp	Leu	Thr	Gln	His	Lys	Phe	Ile	
				170					175					180	
Cys	Glu	Gln	Cys	Gly	Lys	Cys	Lys	Cys	Gly	Glu	Cys	Thr	Ala	Pro	
				185					190					195	
Arg	Thr	Leu	Pro	Ser	Cys	Leu	Ala	Cys	Asn	Arg	Gln	Cys	Leu	Cys	
				200					205					210	
Ser	Ala	Glu	Ser	Met	Val	Glu	Tyr	Gly	Thr	Cys	Met	Cys	Leu	Val	
				215					220					225	
Lys	Gly	Ile	Phe	Tyr	His	Cys	Ser	Asn	Asp	Asp	Glu	Gly	Asp	Ser	
				230					235					240	
Tyr	Ser	Asp	Asn	Pro	Cys	Ser	Cys	Ser	Gln	Ser	His	Cys	Cys	Ser	
				245					250					255	
Arg	Tyr	Leu	Cys	Met	Gly	Ala	Met	Ser	Leu	Phe	Leu	Pro	Cys	Leu	
				260					265					270	
Leu	Cys	Tyr	Pro	Pro	Ala	Lys	Gly	Cys	Leu	Lys	Leu	Cys	Arg	Arg	
				275					280					285	
Cys	Tyr	Asp	Trp	Ile	His	Arg	Pro	Gly	Cys	Arg	Cys	Lys	Asn	Ser	
				290					295					300	
Asn	Thr	Val	Tyr	Cys	Lys	Leu	Glu	Ser	Cys	Pro	Ser	Arg	Gly	Gln	
				305					310					315	

Gly Lys Pro Ser

<210> 10

<211> 747

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2320010CD1

<400> 10

Met	Gly	Lys	Arg	Asn	Ile	Ala	Arg	Val	His	Asp	Ala	Trp	Leu	Ser	
1				5					10					15	
Lys	His	Phe	Gly	Ile	Asp	Arg	Lys	Ser	Gln	Thr	Met	Pro	Ala	Leu	
				20					25					30	
Arg	Asn	Arg	Ser	Gly	Val	Met	Gln	Ala	Arg	Leu	Gln	His	Leu	Ser	
				35					40					45	
Ser	Leu	Glu	Ser	Ser	Phe	Thr	Leu	Asn	His	Ser	Ser	Thr	Thr	Thr	
				50					55					60	
Glu	Ala	Asp	Ile	Phe	His	Gln	Ala	Leu	Leu	Ala	Ala	Asn	Thr	Ala	
				65					70					75	
Thr	Glu	Val	Ser	Leu	Thr	Val	Leu	Asp	Thr	Ile	Ser	Phe	Phe	Thr	
				80					85					90	
Gln	Cys	Phe	Lys	Thr	Gln	Leu	Leu	Asn	Asn	Asp	Gly	His	Asn	Pro	
				95					100					105	
Leu	Met	Lys	Lys	Val	Phe	Asp	Ile	His	Leu	Ala	Phe	Leu	Lys	Asn	
				110					115					120	
Gly	Gln	Ser	Glu	Val	Ser	Leu	Lys	His	Val	Phe	Ala	Ser	Leu	Arg	
				125					130					135	
Ala	Phe	Ile	Ser	Lys	Phe	Pro	Ser	Ala	Phe	Phe	Lys	Gly	Arg	Val	
				140					145					150	
Asn	Met	Cys	Ala	Ala	Phe	Cys	Tyr	Glu	Val	Leu	Lys	Cys	Cys	Thr	
				155					160					165	
Ser	Lys	Ile	Ser	Ser	Thr	Arg	Asn	Glu	Ala	Ser	Ala	Leu	Leu	Tyr	

Leu	Leu	Met	Arg	Asn	Asn	Phe	Glu	Tyr	170	Thr	Lys	Arg	Lys	Thr	175	180
				185						190						Phe
Leu	Arg	Thr	His	Leu	Gln	Ile	Ile	Ile	200	Ala	Val	Ser	Gln	Leu	Ile	195
				215						205						210
Ala	Asp	Val	Ala	Leu	Ser	Gly	Gly	Ser	220	Arg	Phe	Gln	Glu	Ser	Leu	225
				230						235						Ala
Phe	Ile	Ile	Asn	Asn	Phe	Ala	Asn	Ser	245	Asp	Arg	Pro	Met	Lys	Arg	240
				260						250						255
Thr	Ala	Phe	Pro	Ala	Glu	Val	Lys	Asp	265	Leu	Thr	Lys	Arg	Ile	Arg	270
				275						280						285
Thr	Val	Leu	Met	Ala	Thr	Ala	Gln	Met	290	Lys	Glu	His	Glu	Lys	Asp	295
				305						310						Tyr
Pro	Glu	Met	Leu	Ile	Asp	Leu	Gln	Tyr	320	Ser	Leu	Ala	Lys	Ser	Ala	300
				335						340						315
Ala	Ser	Thr	Pro	Glu	Leu	Arg	Lys	Thr	350	Trp	Leu	Asp	Ser	Met	Ala	330
				365						370						345
Lys	Ile	His	Val	Lys	Asn	Gly	Asp	Phe	380	Ser	Glu	Ala	Ala	Met	Cys	360
				395						400						375
Tyr	Val	His	Val	Ala	Ala	Leu	Val	Ala	410	Glu	Phe	Leu	His	Arg	Lys	390
				425						430						405
Lys	Leu	Phe	Pro	Asn	Gly	Cys	Ser	Ala	440	Phe	Lys	Lys	Ile	Thr	Pro	420
				455						460						435
Asn	Ile	Asp	Glu	Glu	Gly	Ala	Met	Lys	470	Glu	Asp	Ala	Gly	Met	Met	450
				485						490						465
Asp	Val	His	Tyr	Ser	Glu	Glu	Val	Leu	500	Leu	Glu	Leu	Leu	Glu	Gln	480
				515						520						495
Cys	Val	Asp	Gly	Leu	Trp	Lys	Ala	Glu	530	Arg	Tyr	Glu	Ile	Ile	Ser	510
				545						550						525
Glu	Ile	Ser	Lys	Leu	Ile	Val	Pro	Ile	560	Tyr	Glu	Lys	Arg	Arg	Glu	540
				575						580						555
Phe	Glu	Lys	Leu	Thr	Gln	Val	Tyr	Arg	590	Thr	Leu	His	Gly	Ala	Tyr	570
				605						610						585
Thr	Lys	Ile	Leu	Glu	Val	Met	His	Thr	620	Lys	Lys	Arg	Leu	Leu	Gly	600
				635						640						615
Thr	Phe	Phe	Arg	Val	Ala	Phe	Tyr	Gly	650	Gln	Ser	Phe	Phe	Glu	Glu	630
				665						670						645
Glu	Asp	Gly	Lys	Glu	Tyr	Ile	Tyr	Lys	680	Glu	Pro	Lys	Leu	Thr	Gly	660
				695						700						675
Leu	Ser	Glu	Ile	Ser	Leu	Arg	Leu	Val	710	Lys	Leu	Tyr	Gly	Glu	Lys	700
				725						730						715
Phe	Gly	Thr	Glu	Asn	Val	Lys	Ile	Ile	740	Gln	Asp	Ser	Asp	Lys	Val	730
				755						760						745
Asn	Ala	Lys	Glu	Leu	Asp	Pro	Lys	Tyr	770	Ala	His	Ile	Gln	Val	Thr	760
				785						790						775
Tyr	Val	Lys	Pro	Tyr	Phe	Asp	Asp	Lys	800	Glu	Leu	Thr	Glu	Arg	Lys	790
				815						820						805
Thr	Glu	Phe	Glu	Arg	Asn	His	Asn	Ile	830	Ser	Arg	Phe	Val	Phe	Glu	815
				845						850						830
Ala	Pro	Tyr	Thr	Leu	Ser	Gly	Lys	Lys	860	Gln	Gly	Cys	Ile	Glu	Glu	845
				875						880						860
Gln	Cys	Lys	Arg	Arg	Thr	Ile	Leu	Thr	890	Thr	Ser	Asn	Ser	Phe	Pro	875
				905						910						890
Tyr	Val	Lys	Lys	Arg	Ile	Pro	Ile	Asn	920	Cys	Glu	Gln	Gln	Ile	Asn	905
				935						940						920
Leu	Lys	Pro	Ile	Asp	Val	Ala	Thr	Asp	950	Glu	Ile	Lys	Asp	Lys	Thr	935
				965						970						950
Ala	Glu	Leu	Gln	Lys	Leu	Cys	Ser	Ser	980	Thr	Asp	Val	Asp	Met	Ile	965
				995						1000						980
Gln	Leu	Gln	Leu	Lys	Leu	Gln	Gly	Cys	1010	Val	Ser	Val	Gln	Val	Asn	995
				1025						1030						1010
Ala	Gly	Pro	Leu	Ala	Tyr	Ala	Arg	Ala	1040	Phe	Leu	Asn	Asp	Ser	Gln	1025
				1055						1060						1040
Ala	Ser	Lys	Tyr	Pro	Pro	Lys	Lys	Val	1070	Ser	Glu	Leu	Lys	Asp	Met	1055
				1085						1090						1070
Phe	Arg	Lys	Phe	Ile	Gln	Ala	Cys	Ser	1100	Ile	Ala	Leu	Glu	Leu	Asn	1085
				1115						1120						1100

Glu	Arg	Leu	Ile	Lys	Glu	Asp	Gln	Val	Glu	Tyr	His	Glu	Gly	Leu
				680					685					690
Lys	Ser	Asn	Phe	Arg	Asp	Met	Val	Lys	Glu	Leu	Ser	Asp	Ile	Ile
				695					700					705
His	Glu	Gln	Ile	Leu	Gln	Glu	Asp	Thr	Met	His	Ser	Pro	Trp	Met
				710					715					720
Ser	Asn	Thr	Leu	His	Val	Phe	Cys	Ala	Ile	Ser	Gly	Thr	Ser	Ser
				725					730					735
Asp	Arg	Gly	Tyr	Gly	Ser	Pro	Arg	Tyr	Ala	Glu	Val			
				740					745					

<210> 11

<211> 266

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2564901CD1

<400> 11

Met	Gln	Gly	Ser	Thr	Arg	Arg	Met	Gly	Val	Met	Thr	Asp	Val	His
1				5					10					15
Arg	Arg	Phe	Leu	Gln	Leu	Leu	Met	Thr	His	Gly	Val	Leu	Glu	Glu
				20					25					30
Trp	Asp	Val	Lys	Arg	Leu	Gln	Thr	His	Cys	Tyr	Lys	Val	His	Asp
				35					40					45
Arg	Asn	Ala	Thr	Val	Asp	Lys	Leu	Glu	Asp	Phe	Ile	Asn	Asn	Ile
				50					55					60
Asn	Ser	Val	Leu	Glu	Ser	Leu	Tyr	Ile	Glu	Ile	Lys	Arg	Gly	Val
				65					70					75
Thr	Glu	Asp	Asp	Gly	Arg	Pro	Ile	Tyr	Ala	Leu	Val	Asn	Leu	Ala
				80					85					90
Thr	Thr	Ser	Ile	Ser	Lys	Met	Ala	Thr	Asp	Phe	Ala	Glu	Asn	Glu
				95					100					105
Leu	Asp	Leu	Phe	Arg	Lys	Ala	Leu	Glu	Leu	Ile	Ile	Asp	Ser	Glu
				110					115					120
Thr	Gly	Phe	Ala	Ser	Ser	Thr	Asn	Ile	Leu	Asn	Leu	Val	Asp	Gln
				125					130					135
Leu	Lys	Gly	Lys	Lys	Met	Arg	Lys	Lys	Glu	Ala	Glu	Gln	Val	Leu
				140					145					150
Gln	Lys	Phe	Val	Gln	Asn	Lys	Trp	Leu	Ile	Glu	Lys	Glu	Gly	Glu
				155					160					165
Phe	Thr	Leu	His	Gly	Arg	Ala	Ile	Leu	Glu	Met	Glu	Gln	Tyr	Ile
				170					175					180
Arg	Glu	Thr	Tyr	Pro	Asp	Ala	Val	Lys	Ile	Cys	Asn	Ile	Cys	His
				185					190					195
Ser	Leu	Leu	Ile	Gln	Gly	Gln	Ser	Cys	Glu	Thr	Cys	Gly	Ile	Arg
				200					205					210
Met	His	Leu	Pro	Cys	Val	Ala	Lys	Tyr	Phe	Gln	Ser	Asn	Ala	Glu
				215					220					225
Pro	Arg	Cys	Pro	His	Cys	Asn	Asp	Tyr	Trp	Pro	His	Glu	Ile	Pro
				230					235					240
Lys	Val	Phe	Asp	Pro	Glu	Lys	Glu	Arg	Glu	Ser	Gly	Val	Leu	Lys
				245					250					255
Ser	Asn	Lys	Lys	Ser	Leu	Arg	Ser	Arg	Gln	His				
				260					265					

<210> 12

<211> 345

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2615168CD1

<400> 12

Met	Ser	Val	Thr	Gly	Gly	Lys	Met	Ala	Pro	Ser	Leu	Thr	Gln	Glu
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

1	5	10	15
Ile Leu Ser His	Leu Gly Leu Ala Ser	Lys Thr Ala Ala Trp	Gly
20	25	30	
Thr Leu Gly Thr	Leu Arg Thr Phe Leu	Asn Phe Ser Val Asp	Lys
35	40	45	
Asp Ala Gln Arg	Leu Leu Arg Ala Ile	Thr Gly Gln Gly Val	Asp
50	55	60	
Arg Ser Ala Ile	Val Asp Val Leu Thr	Asn Arg Ser Arg Glu	Gln
65	70	75	
Arg Gln Leu Ile	Ser Arg Asn Phe Gln	Glu Arg Thr Gln Gln	Asp
80	85	90	
Leu Met Lys Ser	Leu Gln Ala Ala Leu	Ser Gly Asn Leu Glu	Arg
95	100	105	
Ile Val Met Ala	Leu Leu Gln Pro Thr	Ala Gln Phe Asp Ala	Gln
110	115	120	
Glu Leu Arg Thr	Ala Leu Lys Ala Ser	Asp Ser Ala Val Asp	Val
125	130	135	
Ala Ile Glu Ile	Leu Ala Thr Arg Thr	Pro Gln Leu Gln	Glu
140	145	150	
Cys Leu Ala Val	Tyr Lys His Asn Phe	Gln Val Glu Ala Val	Asp
155	160	165	
Asp Ile Thr Ser	Glu Thr Ser Gly Ile	Leu Gln Asp Leu Leu	Leu
170	175	180	
Ala Leu Ala Lys	Gly Gly Arg Asp Ser	Tyr Ser Gly Ile Ile	Asp
185	190	195	
Tyr Asn Leu Ala	Glu Gln Asp Val Gln	Ala Leu Gln Arg Ala	Glu
200	205	210	
Gly Pro Ser Arg	Glu Glu Thr Trp Val	Pro Val Phe Thr Gln	Arg
215	220	225	
Asn Pro Glu His	Leu Ile Arg Val Phe	Asp Gln Tyr Gln Arg	Ser
230	235	240	
Thr Gly Gln Glu	Leu Glu Glu Ala Val	Gln Asn Arg Phe His	Gly
245	250	255	
Asp Ala Gln Val	Ala Leu Leu Gly Leu	Ala Ser Val Ile Lys	Asn
260	265	270	
Thr Pro Leu Tyr	Phe Ala Asp Lys Leu	His Gln Ala Leu Gln	Glu
275	280	285	
Thr Glu Pro Asn	Tyr Gln Val Leu Ile	Arg Ile Leu Ile Ser	Arg
290	295	300	
Cys Glu Thr Asp	Leu Leu Ser Ile Arg	Ala Glu Phe Arg Lys	Lys
305	310	315	
Phe Gly Lys Ser	Leu Tyr Ser Ser Leu	Gln Asp Ala Val Lys	Gly
320	325	330	
Asp Cys Gln Ser	Ala Leu Leu Ala Leu	Cys Arg Ala Glu Asp	Met
335	340	345	

<210> 13

<211> 437

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2658329CD1

<400> 13

Met Glu Lys Glu	Leu Arg Ser Thr Ile	Leu Phe Asn Ala Tyr	Lys
1	5	10	15
Lys Glu Ile Phe	Thr Thr Asn Asn Gly	Tyr Lys Ser Met Gln	Lys
20	25	30	
Lys Leu Arg Ser	Asn Trp Lys Ile Gln	Ser Leu Lys Asp Glu	Ile
35	40	45	
Thr Ser Glu Lys	Leu Asn Gly Val Lys	Leu Trp Ile Thr Ala	Gly
50	55	60	
Pro Arg Glu Lys	Phe Thr Ala Ala Glu	Phe Glu Ile Leu Lys	Lys
65	70	75	
Tyr Leu Asp Thr	Gly Gly Asp Val Phe	Val Met Leu Gly Glu	Gly

	80		85		90
Gly Glu Ser Arg	Phe Asp Thr Asn Ile	Asn Phe Leu Leu Glu	Glu		
	95	100			105
Tyr Gly Ile Met	Val Asn Asn Asp Ala	Val Val Arg Asn Val	Tyr		
	110	115			120
His Lys Tyr Phe	His Pro Lys Glu Ala	Leu Val Ser Ser Gly	Val		
	125	130			135
Leu Asn Arg Glu	Ile Ser Arg Ala Ala	Gly Lys Ala Val Pro	Gly		
	140	145			150
Ile Ile Asp Glu	Glu Ser Ser Gly Asn	Asn Ala Gln Ala Leu	Thr		
	155	160			165
Phe Val Tyr Pro	Phe Gly Ala Thr Leu	Ser Val Met Lys Pro	Ala		
	170	175			180
Val Ala Val Leu	Ser Thr Gly Ser Val	Cys Phe Pro Leu Asn	Arg		
	185	190			195
Pro Ile Leu Ala	Phe Tyr His Ser Lys	Asn Gln Gly Gly Lys	Leu		
	200	205			210
Ala Val Leu Gly	Ser Cys His Met Phe	Ser Asp Gln Tyr Leu	Asp		
	215	220			225
Lys Glu Glu Asn	Ser Lys Ile Met Asp	Val Val Phe Gln Trp	Leu		
	230	235			240
Thr Thr Gly Asp	Ile His Leu Asn Gln	Ile Asp Ala Glu Asp	Pro		
	245	250			255
Glu Ile Ser Asp	Tyr Met Met Leu Pro	Tyr Thr Ala Thr Leu	Ser		
	260	265			270
Lys Arg Asn Arg	Glu Cys Leu Gln Glu	Ser Asp Glu Ile Pro	Arg		
	275	280			285
Asp Phe Thr Thr	Leu Phe Asp Leu Ser	Ile Phe Gln Leu Asp	Thr		
	290	295			300
Thr Ser Phe His	Ser Val Ile Glu Ala	His Glu Gln Leu Asn	Val		
	305	310			315
Lys His Glu Pro	Leu Gln Leu Ile Gln	Pro Gln Phe Glu Thr	Pro		
	320	325			330
Leu Pro Thr Leu	Gln Pro Ala Val Phe	Pro Pro Ser Phe Arg	Glu		
	335	340			345
Leu Pro Pro Pro	Pro Leu Glu Leu Phe	Asp Leu Asp Glu Thr	Phe		
	350	355			360
Ser Ser Glu Lys	Ala Arg Leu Ala Gln	Ile Thr Asn Lys Cys	Thr		
	365	370			375
Glu Glu Asp Leu	Glu Phe Tyr Val Arg	Lys Cys Gly Asp Ile	Leu		
	380	385			390
Gly Val Thr Ser	Lys Leu Pro Lys Asp	Gln Gln Asp Ala Lys	His		
	395	400			405
Ile Leu Glu His	Val Phe Phe Gln Val	Val Glu Phe Lys Lys	Leu		
	410	415			420
Asn Gln Glu His	Asp Ile Asp Thr Ser	Glu Thr Ala Phe Gln	Asn		
	425	430			435

Asn Phe

<210> 14

<211> 441

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2708944CD1

<400> 14

Met Val His Ile	Lys Lys Gly Glu Leu Thr	Gln Glu Glu Lys Glu		
1	5	10	15	
Leu Leu Glu Val	Ile Gly Lys Gly Thr Val	Gln Glu Ala Gly Thr		
	20	25	30	
Leu Leu Ser Ser	Lys Asn Val Arg Val Asn	Cys Leu Asp Glu Asn		
	35	40	45	
Gly Met Thr Pro	Leu Met His Ala Ala Tyr	Lys Gly Lys Leu Asp		
	50	55	60	

Met	Cys	Lys	Leu	Leu	Leu	Arg	His	Gly	Ala	Asp	Val	Asn	Cys	His	
				65					70						75
Gln	His	Glu	His	Gly	Tyr	Thr	Ala	Leu	Met	Phe	Ala	Ala	Leu	Ser	
				80					85						90
Gly	Asn	Lys	Asp	Ile	Thr	Trp	Val	Met	Leu	Glu	Ala	Gly	Ala	Glu	
				95					100						105
Thr	Asp	Val	Val	Asn	Ser	Val	Gly	Arg	Thr	Ala	Ala	Gln	Met	Ala	
				110					115						120
Ala	Phe	Val	Gly	Gln	His	Asp	Cys	Val	Thr	Ile	Ile	Asn	Asn	Phe	
				125					130						135
Phe	Pro	Arg	Glu	Arg	Leu	Asp	Tyr	Tyr	Thr	Lys	Pro	Gln	Gly	Leu	
				140					145						150
Asp	Lys	Glu	Pro	Lys	Leu	Pro	Pro	Lys	Leu	Ala	Gly	Pro	Leu	His	
				155					160						165
Lys	Ile	Ile	Thr	Thr	Thr	Asn	Leu	His	Pro	Val	Lys	Ile	Val	Met	
				170					175						180
Leu	Val	Asn	Glu	Asn	Pro	Leu	Leu	Thr	Glu	Glu	Ala	Ala	Leu	Asn	
				185					190						195
Lys	Cys	Tyr	Arg	Val	Met	Asp	Leu	Ile	Cys	Glu	Lys	Cys	Met	Lys	
				200					205						210
Gln	Arg	Asp	Met	Asn	Glu	Val	Leu	Ala	Met	Lys	Met	His	Tyr	Ile	
				215					220						225
Ser	Cys	Ile	Phe	Gln	Lys	Cys	Ile	Asn	Phe	Leu	Lys	Asp	Gly	Glu	
				230					235						240
Asn	Lys	Leu	Asp	Thr	Leu	Ile	Lys	Ser	Leu	Leu	Lys	Gly	Arg	Ala	
				245					250						255
Ser	Asp	Gly	Phe	Pro	Val	Tyr	Gln	Glu	Lys	Ile	Ile	Arg	Glu	Ser	
				260					265						270
Ile	Arg	Lys	Phe	Pro	Tyr	Cys	Glu	Ala	Thr	Leu	Leu	Gln	Gln	Leu	
				275					280						285
Val	Arg	Ser	Ile	Ala	Pro	Val	Glu	Ile	Gly	Ser	Asp	Pro	Thr	Ala	
				290					295						300
Phe	Ser	Val	Leu	Thr	Gln	Ala	Ile	Thr	Gly	Gln	Val	Gly	Phe	Val	
				305					310						315
Asp	Val	Glu	Phe	Cys	Thr	Thr	Cys	Gly	Glu	Lys	Gly	Ala	Ser	Lys	
				320					325						330
Arg	Cys	Ser	Val	Cys	Lys	Met	Val	Ile	Tyr	Cys	Asp	Gln	Thr	Cys	
				335					340						345
Gln	Lys	Thr	His	Trp	Phe	Thr	His	Lys	Lys	Ile	Cys	Lys	Asn	Leu	
				350					355						360
Lys	Asp	Ile	Tyr	Glu	Lys	Gln	Gln	Leu	Glu	Ala	Ala	Lys	Glu	Lys	
				365					370						375
Arg	Gln	Glu	Glu	Asn	His	Gly	Lys	Leu	Asp	Val	Asn	Ser	Asn	Cys	
				380					385						390
Val	Asn	Glu	Glu	Gln	Pro	Glu	Ala	Glu	Val	Gly	Ile	Ser	Gln	Lys	
				395					400						405
Asp	Ser	Asn	Pro	Glu	Asp	Ser	Gly	Glu	Gly	Lys	Lys	Glu	Ser	Leu	
				410					415						420
Glu	Ser	Glu	Ala	Glu	Leu	Glu	Gly	Leu	Gln	Asp	Ala	Pro	Ala	Gly	
				425					430						435
Pro	Gln	Val	Ser	Glu	Glu										
				440											

<210> 15

<211> 487

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3315012CD1

<400> 15

Met	Leu	Arg	Ala	Pro	Gly	Cys	Leu	Leu	Arg	Thr	Ser	Val	Ala	Pro	
1				5					10						15
Ala	Ala	Ala	Leu	Ala	Ala	Ala	Leu	Leu	Ser	Ser	Leu	Ala	Arg	Cys	
				20					25						30
Ser	Leu	Leu	Glu	Pro	Arg	Asp	Pro	Val	Ala	Ser	Ser	Leu	Ser	Pro	

	35		40		45
Tyr Phe Gly Thr	Lys Thr Arg Tyr Glu Asp	Val Asn Pro Val	Leu		
	50		55		60
Leu Ser Gly Pro	Glu Ala Pro Trp Arg Asp	Pro Glu Leu Leu	Glu		
	65		70		75
Gly Thr Cys Thr	Pro Val Gln Leu Val Ala	Leu Ile Arg His	Gly		
	80		85		90
Thr Arg Tyr Pro	Thr Val Lys Gln Ile Arg	Lys Leu Arg Gln	Leu		
	95		100		105
His Gly Leu Leu	Gln Ala Arg Gly Ser Arg	Asp Gly Gly Ala	Ser		
	110		115		120
Ser Thr Gly Ser	Arg Asp Leu Gly Ala Ala	Leu Ala Asp Trp	Pro		
	125		130		135
Leu Trp Tyr Ala	Asp Trp Met Asp Gly Gln	Leu Val Glu Lys	Gly		
	140		145		150
Arg Gln Asp Met	Arg Gln Leu Ala Leu Arg	Leu Ala Ser Leu	Phe		
	155		160		165
Pro Val Leu Phe	Ser Arg Glu Asn Tyr Gly	Arg Leu Arg Leu	Ile		
	170		175		180
Thr Ser Ser Lys	His Arg Cys Met Asp Ser	Ser Ala Ala Phe	Leu		
	185		190		195
Gln Gly Leu Trp	Gln His Tyr His Pro Gly	Leu Pro Pro Pro	Asp		
	200		205		210
Val Ala Asp Met	Glu Phe Gly Pro Pro Thr	Val Asn Asp Lys	Leu		
	215		220		225
Met Arg Phe Phe	Asp His Cys Glu Lys Phe	Leu Thr Glu Val	Glu		
	230		235		240
Lys Asn Ala Thr	Ala Leu Tyr His Val Glu	Ala Phe Lys Thr	Gly		
	245		250		255
Pro Glu Met Gln	Asn Ile Leu Lys Lys Val	Ala Ala Thr Leu	Gln		
	260		265		270
Val Pro Val Asn	Asp Leu Asn Ala Asp Leu	Ile Gln Val Ala	Phe		
	275		280		285
Phe Thr Cys Ser	Phe Asp Leu Ala Ile Lys	Gly Val Lys Ser	Pro		
	290		295		300
Trp Cys Asp Val	Phe Asp Ile Asp Asp Ala	Lys Val Leu Glu	Tyr		
	305		310		315
Leu Asn Asp Leu	Lys Gln Tyr Trp Lys Arg	Gly Tyr Gly Tyr	Thr		
	320		325		330
Ile Asn Ser Arg	Ser Ser Cys Thr Leu Phe	Gln Asp Ile Phe	Gln		
	335		340		345
His Leu Asp Lys	Ala Val Glu Gln Lys Gln	Arg Ser Gln Pro	Ile		
	350		355		360
Ser Ser Pro Val	Ile Leu Gln Phe Gly His	Ala Glu Thr Leu	Leu		
	365		370		375
Pro Leu Leu Ser	Leu Met Gly Tyr Phe Lys	Asp Lys Glu Pro	Leu		
	380		385		390
Thr Ala Tyr Asn	Tyr Lys Lys Gln Met His	Arg Lys Phe Arg	Ser		
	395		400		405
Gly Leu Ile Val	Pro Tyr Ala Ser Asn Leu	Ile Phe Val Leu	Tyr		
	410		415		420
His Cys Glu Asn	Ala Lys Thr Pro Lys Glu	Gln Phe Arg Val	Gln		
	425		430		435
Met Leu Leu Asn	Glu Lys Val Leu Pro Leu	Ala Tyr Ser Gln	Glu		
	440		445		450
Thr Val Ser Phe	Tyr Glu Asp Leu Lys Asn	His Tyr Lys Asp	Ile		
	455		460		465
Leu Gln Ser Cys	Gln Thr Ser Glu Glu Cys	Glu Leu Ala Arg	Ala		
	470		475		480
Asn Ser Thr Ser	Asp Glu Leu				
	485				

<210> 16

<211> 282

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature
 <223> Incyte ID No: 4155412CD1

<400> 16

Met	Val	Leu	Gly	Lys	Val	Lys	Ser	Leu	Thr	Ile	Ser	Phe	Asp	Cys	
1				5					10					15	
Leu	Asn	Asp	Ser	Asn	Val	Pro	Val	Tyr	Ser	Ser	Gly	Asp	Thr	Val	
				20					25					30	
Ser	Gly	Arg	Val	Asn	Leu	Glu	Val	Thr	Gly	Glu	Ile	Arg	Val	Lys	
				35					40					45	
Ser	Leu	Lys	Ile	His	Ala	Arg	Gly	His	Ala	Lys	Val	Arg	Trp	Thr	
				50					55					60	
Glu	Ser	Arg	Asn	Ala	Gly	Ser	Asn	Thr	Ala	Tyr	Thr	Gln	Asn	Tyr	
				65					70					75	
Thr	Glu	Glu	Val	Glu	Tyr	Phe	Asn	His	Lys	Asp	Ile	Leu	Ile	Gly	
				80					85					90	
His	Glu	Arg	Asp	Asp	Asn	Ser	Glu	Glu	Gly	Phe	His	Thr	Ile		
				95					100					105	
His	Ser	Gly	Arg	His	Glu	Tyr	Ala	Phe	Ser	Phe	Glu	Leu	Pro	Gln	
				110					115					120	
Thr	Pro	Leu	Ala	Thr	Ser	Phe	Glu	Gly	Arg	His	Gly	Ser	Val	Arg	
				125					130					135	
Tyr	Trp	Val	Lys	Ala	Glu	Leu	His	Arg	Pro	Trp	Leu	Leu	Pro	Val	
				140					145					150	
Lys	Leu	Lys	Lys	Glu	Phe	Thr	Val	Phe	Glu	His	Ile	Asp	Ile	Asn	
				155					160					165	
Thr	Pro	Ser	Leu	Leu	Ser	Pro	Gln	Ala	Gly	Thr	Lys	Glu	Lys	Thr	
				170					175					180	
Leu	Cys	Cys	Trp	Phe	Cys	Thr	Ser	Gly	Pro	Ile	Ser	Leu	Ser	Ala	
				185					190					195	
Lys	Ile	Glu	Arg	Lys	Gly	Tyr	Thr	Pro	Gly	Glu	Ser	Ile	Gln	Ile	
				200					205					210	
Phe	Ala	Glu	Ile	Glu	Asn	Cys	Ser	Ser	Arg	Met	Val	Val	Pro	Arg	
				215					220					225	
Gln	Pro	Phe	Thr	Lys	His	Arg	Pro	Ser	Ile	Ala	Lys	Gly	Lys	Leu	
				230					235					240	
Arg	Glu	Leu	Asn	Ser	Leu	Trp	Leu	Thr	Cys	Val	Gly	Asn	Ser	Leu	
				245					250					255	
Thr	Ser	Gly	Lys	Asn	Arg	Asp	Val	Glu	Met	Ala	Ser	Leu	Leu	Lys	
				260					265					270	
Ile	Ser	Asn	Ser	Phe	Pro	Pro	Ser	Asn	Ala	Ser	Asn				
				275					280						

<210> 17

<211> 581

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 4831840CD1

<400> 17

Met	Ala	Val	Ala	Gly	Ala	Val	Ser	Gly	Glu	Pro	Leu	Val	His	Trp	
1				5					10					15	
Cys	Thr	Gln	Gln	Leu	Arg	Lys	Thr	Phe	Gly	Leu	Asp	Val	Ser	Glu	
				20					25					30	
Glu	Ile	Ile	Gln	Tyr	Val	Leu	Ser	Ile	Glu	Ser	Ala	Glu	Glu	Ile	
				35					40					45	
Arg	Glu	Tyr	Val	Thr	Asp	Leu	Leu	Gln	Gly	Asn	Glu	Gly	Lys	Lys	
				50					55					60	
Gly	Gln	Phe	Ile	Glu	Glu	Leu	Ile	Thr	Lys	Trp	Gln	Lys	Asn	Asp	
				65					70					75	
Gln	Glu	Leu	Ile	Ser	Asp	Pro	Leu	Gln	Gln	Cys	Phe	Lys	Lys	Asp	
				80					85					90	
Glu	Ile	Leu	Asp	Gly	Gln	Lys	Ser	Gly	Asp	His	Leu	Lys	Arg	Gly	
				95					100					105	
Arg	Lys	Lys	Gly	Arg	Asn	Arg	Gln	Glu	Val	Pro	Ala	Phe	Thr	Glu	

Pro Asp Thr Thr	110	115	120
Ala Glu Val Lys Thr	125	Pro Phe Asp Leu Ala Lys	135
Ala Gln Glu Asn Ser Asn Ser Val Lys	140	Lys Thr Lys Phe Val	150
Asn Leu Tyr Thr Arg Glu Gly Gln Asp	155	Arg Leu Ala Val Leu Leu	165
Pro Gly Arg His Pro Cys Asp Cys Leu	170	Gly Gln Lys His Lys Leu	180
Ile Asn Asn Cys Leu Ile Cys Gly Arg	185	Ile Val Cys Glu Gln Glu	195
Gly Ser Gly Pro Cys Leu Phe Cys Gly	200	Thr Leu Val Cys Thr His	210
Glu Glu Gln Asp Ile Leu Gln Arg Asp	215	Ser Asn Lys Ser Gln Lys	225
Leu Leu Lys Lys Leu Met Ser Gly Val	230	Glu Asn Ser Gly Lys Val	240
Asp Ile Ser Thr Lys Asp Leu Leu Pro	245	His Gln Glu Leu Arg Ile	255
Lys Ser Gly Leu Glu Lys Ala Ile Lys	260	His Lys Asp Lys Leu Leu	270
Glu Phe Asp Arg Thr Ser Ile Arg Arg	275	Thr Gln Val Ile Asp Asp	285
Glu Ser Asp Tyr Phe Ala Ser Asp Ser	290	Asn Gln Trp Leu Ser Lys	300
Leu Glu Arg Glu Thr Leu Gln Lys Arg	305	Glu Glu Glu Leu Arg Glu	315
Leu Arg His Ala Ser Arg Leu Ser Lys	320	Lys Val Thr Ile Asp Phe	330
Ala Gly Arg Lys Ile Leu Glu Glu Glu	335	Asn Ser Leu Ala Glu Tyr	345
His Ser Arg Leu Asp Glu Thr Ile Gln	350	Ala Ile Ala Asn Gly Thr	360
Leu Asn Gln Pro Leu Thr Lys Leu Asp	365	Arg Ser Ser Glu Glu Pro	375
Leu Gly Val Leu Val Asn Pro Asn Met	380	Tyr Gln Ser Pro Pro Gln	390
Trp Val Asp His Thr Gly Ala Ala Ser	395	Gln Lys Lys Ala Phe Arg	405
Ser Ser Gly Phe Gly Leu Glu Phe Asn	410	Ser Phe Gln His Gln Leu	420
Arg Ile Gln Asp Gln Glu Phe Gln Glu	425	Gly Phe Asp Gly Gly Trp	435
Cys Leu Ser Val His Gln Pro Trp Ala	440	Ser Leu Leu Val Arg Gly	450
Ile Lys Arg Val Glu Gly Arg Ser Trp	455	Tyr Thr Pro His Arg Gly	465
Arg Leu Trp Ile Ala Ala Thr Ala Lys	470	Lys Pro Ser Pro Gln Glu	480
Val Ser Glu Leu Gln Ala Thr Tyr Arg	485	Leu Leu Arg Gly Lys Asp	495
Val Glu Phe Pro Asn Asp Tyr Pro Ser	500	Gly Cys Leu Leu Gly Cys	510
Val Asp Leu Ile Asp Cys Leu Ser Gln	515	Lys Gln Phe Lys Glu Gln	525
Phe Pro Asp Ile Ser Gln Glu Ser Asp	530	Ser Pro Phe Val Phe Ile	540
Cys Lys Asn Pro Gln Glu Met Val Val	545	Lys Phe Pro Ile Lys Gly	555
Asn Pro Lys Ile Trp Lys Leu Asp Ser	560	Lys Ile His Gln Gly Ala	570
Lys Lys Gly Leu Met Lys Gln Asn Lys	575	Ala Val	580

<210> 18

<211> 530

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 5676581CD1

<400> 18

Met	Thr	Thr	Arg	Pro	Thr	Ala	Val	Lys	Ala	Thr	Gly	Gly	Leu	Cys
1				5					10					15
Leu	Leu	Gly	Ala	Tyr	Ala	Asp	Ser	Asp	Asp	Asp	Asp	Asn	Asp	Val
				20					25					30
Ser	Glu	Lys	Leu	Ala	Gln	Ser	Lys	Glu	Thr	Asn	Gly	Asn	Gln	Ser
				35					40					45
Thr	Asp	Ile	Asp	Ser	Thr	Leu	Ala	Asn	Phe	Leu	Ala	Glu	Ile	Asp
				50					55					60
Ala	Ile	Thr	Ala	Pro	Gln	Pro	Ala	Ala	Pro	Val	Gly	Ala	Ser	Ala
				65					70					75
Pro	Pro	Pro	Thr	Pro	Pro	Arg	Pro	Glu	Pro	Lys	Glu	Ala	Ala	Thr
				80					85					90
Ser	Thr	Leu	Ser	Ser	Ser	Thr	Ser	Asn	Gly	Thr	Asp	Ser	Thr	Gln
				95					100					105
Thr	Ser	Gly	Trp	Gln	Tyr	Asp	Thr	Gln	Cys	Ser	Leu	Ala	Gly	Val
				110					115					120
Gly	Ile	Glu	Met	Gly	Asp	Trp	Gln	Glu	Val	Trp	Asp	Glu	Asn	Thr
				125					130					135
Gly	Cys	Tyr	Tyr	Tyr	Trp	Asn	Thr	Gln	Thr	Asn	Glu	Val	Thr	Trp
				140					145					150
Glu	Leu	Pro	Gln	Tyr	Leu	Ala	Thr	Gln	Val	Gln	Gly	Leu	Gln	His
				155					160					165
Tyr	Gln	Pro	Ser	Ser	Val	Pro	Gly	Ala	Glu	Thr	Ser	Phe	Val	Val
				170					175					180
Asn	Thr	Asp	Ile	Tyr	Ser	Lys	Glu	Lys	Thr	Ile	Ser	Val	Ser	Ser
				185					190					195
Ser	Lys	Ser	Gly	Pro	Val	Ile	Ala	Lys	Arg	Glu	Val	Lys	Lys	Glu
				200					205					210
Val	Asn	Glu	Gly	Ile	Gln	Ala	Leu	Ser	Asn	Ser	Glu	Glu	Glu	Lys
				215					220					225
Lys	Gly	Val	Ala	Ala	Ser	Leu	Leu	Ala	Pro	Leu	Leu	Pro	Glu	Gly
				230					235					240
Ile	Lys	Glu	Glu	Glu	Glu	Arg	Trp	Arg	Arg	Lys	Val	Ile	Cys	Lys
				245					250					255
Glu	Glu	Pro	Val	Ser	Glu	Val	Lys	Glu	Thr	Ser	Thr	Thr	Val	Glu
				260					265					270
Glu	Ala	Thr	Thr	Ile	Val	Lys	Pro	Gln	Glu	Ile	Met	Leu	Asp	Asn
				275					280					285
Ile	Glu	Asp	Pro	Ser	Gln	Glu	Asp	Leu	Cys	Ser	Val	Val	Gln	Ser
				290					295					300
Gly	Glu	Ser	Glu	Glu	Glu	Glu	Gln	Asp	Thr	Leu	Glu	Leu	Glu	Glu
				305					310					315
Leu	Val	Leu	Glu	Arg	Lys	Lys	Ala	Glu	Leu	Arg	Ala	Leu	Glu	Glu
				320					325					330
Gly	Asp	Gly	Ser	Val	Ser	Gly	Ser	Ser	Pro	Arg	Ser	Asp	Ile	Ser
				335					340					345
Gln	Pro	Ala	Ser	Gln	Asp	Gly	Met	Arg	Arg	Leu	Met	Ser	Lys	Arg
				350					355					360
Gly	Lys	Trp	Lys	Met	Phe	Val	Arg	Ala	Thr	Ser	Pro	Glu	Ser	Thr
				365					370					375
Ser	Arg	Ser	Ser	Ser	Lys	Thr	Gly	Arg	Asp	Thr	Pro	Glu	Asn	Gly
				380					385					390
Glu	Thr	Ala	Ile	Gly	Ala	Glu	Asn	Ser	Glu	Lys	Ile	Asp	Glu	Asn
				395					400					405
Ser	Asp	Lys	Glu	Met	Glu	Val	Glu	Glu	Ser	Pro	Glu	Lys	Ile	Lys
				410					415					420
Val	Gln	Thr	Thr	Pro	Lys	Val	Glu	Glu	Glu	Gln	Asp	Leu	Lys	Phe
				425					430					435
Gln	Ile	Gly	Glu	Leu	Ala	Asn	Thr	Leu	Thr	Ser	Lys	Phe	Glu	Phe
				440					445					450
Leu	Gly	Ile	Asn	Arg	Gln	Ser	Ile	Ser	Asn	Phe	His	Val	Leu	Leu
				455					460					465

Leu	Gln	Thr	Glu	Thr	Arg	Ile	Ala	Asp	Trp	Arg	Glu	Gly	Ala	Leu
				470					475					480
Asn	Gly	Asn	Tyr	Leu	Lys	Arg	Lys	Leu	Gln	Asp	Ala	Ala	Glu	Gln
				485					490					495
Leu	Lys	Gln	Tyr	Glu	Ile	Asn	Ala	Thr	Pro	Lys	Gly	Trp	Ser	Cys
				500					505					510
His	Trp	Asp	Arg	Tyr	Ala	Leu	Phe	Ser	Pro	Phe	His	Leu	Ser	Pro
				515					520					525
Leu	Thr	Ser	Gln	Thr										
				530										

<210> 19

<211> 475

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 034159CD1

<400> 19

Met	Gln	Lys	Ser	Thr	Asn	Ser	Asp	Thr	Ser	Val	Glu	Thr	Leu	Asn
1				5					10					15
Ser	Thr	Arg	Gln	Gly	Thr	Gly	Ala	Val	Gln	Met	Arg	Ile	Lys	Asn
				20					25					30
Ala	Asn	Ser	His	His	Asp	Arg	Leu	Ser	Gln	Ser	Lys	Ser	Met	Ile
				35					40					45
Leu	Thr	Asp	Val	Gly	Lys	Val	Thr	Glu	Pro	Ile	Ser	Arg	His	Arg
				50					55					60
Arg	Asn	His	Ser	Gln	His	Ile	Leu	Lys	Asp	Val	Ile	Pro	Pro	Leu
				65					70					75
Glu	Gln	Leu	Met	Val	Glu	Lys	Glu	Gly	Tyr	Leu	Gln	Lys	Ala	Lys
				80					85					90
Ile	Ala	Asp	Gly	Gly	Lys	Lys	Leu	Arg	Lys	Asn	Trp	Ser	Thr	Ser
				95					100					105
Trp	Ile	Val	Leu	Ser	Ser	Arg	Arg	Ile	Glu	Phe	Tyr	Lys	Glu	Ser
				110					115					120
Lys	Gln	Gln	Ala	Leu	Ser	Asn	Met	Lys	Thr	Gly	His	Lys	Pro	Glu
				125					130					135
Ser	Val	Asp	Leu	Cys	Gly	Ala	His	Ile	Glu	Trp	Ala	Lys	Glu	Lys
				140					145					150
Ser	Ser	Arg	Lys	Asn	Val	Phe	Gln	Ile	Thr	Thr	Val	Ser	Gly	Asn
				155					160					165
Glu	Phe	Leu	Leu	Gln	Ser	Asp	Ile	Asp	Phe	Ile	Ile	Leu	Asp	Trp
				170					175					180
Phe	His	Ala	Ile	Lys	Asn	Ala	Ile	Asp	Arg	Leu	Pro	Lys	Asp	Ser
				185					190					195
Ser	Cys	Pro	Ser	Arg	Asn	Leu	Glu	Leu	Phe	Lys	Ile	Gln	Arg	Ser
				200					205					210
Ser	Ser	Thr	Glu	Leu	Leu	Ser	His	Tyr	Asp	Ser	Asp	Ile	Lys	Glu
				215					220					225
Gln	Lys	Pro	Glu	His	Arg	Lys	Ser	Leu	Met	Phe	Arg	Leu	His	His
				230					235					240
Ser	Ala	Ser	Asp	Thr	Ser	Asp	Lys	Asn	Arg	Val	Lys	Ser	Arg	Leu
				245					250					255
Lys	Lys	Phe	Ile	Thr	Arg	Arg	Pro	Ser	Leu	Lys	Thr	Leu	Gln	Glu
				260					265					270
Lys	Gly	Leu	Ile	Lys	Asp	Gln	Ile	Phe	Gly	Ser	His	Leu	His	Lys
				275					280					285
Val	Cys	Glu	Arg	Glu	Asn	Ser	Thr	Val	Pro	Trp	Phe	Val	Lys	Gln
				290					295					300
Cys	Ile	Glu	Ala	Val	Glu	Lys	Arg	Gly	Leu	Asp	Val	Asp	Gly	Ile
				305					310					315
Tyr	Arg	Val	Ser	Gly	Asn	Leu	Ala	Thr	Ile	Gln	Lys	Leu	Arg	Phe
				320					325					330
Ile	Val	Asn	Gln	Glu	Glu	Lys	Leu	Asn	Leu	Asp	Asp	Ser	Gln	Trp
				335					340					345
Glu	Asp	Ile	His	Val	Val	Thr	Gly	Ala	Leu	Lys	Met	Phe	Phe	Arg

				350					355					360
Glu	Leu	Pro	Glu	Pro	Leu	Phe	Pro	Tyr	Ser	Phe	Phe	Glu	Gln	Phe
				365					370					375
Val	Glu	Ala	Ile	Lys	Lys	Gln	Asp	Asn	Asn	Thr	Arg	Ile	Glu	Ala
				380					385					390
Val	Lys	Ser	Leu	Val	Gln	Lys	Leu	Pro	Pro	Pro	Asn	Arg	Asp	Thr
				395					400					405
Met	Lys	Val	Leu	Phe	Gly	His	Leu	Thr	Lys	Ile	Val	Ala	Lys	Ala
				410					415					420
Ser	Lys	Asn	Leu	Met	Ser	Thr	Gln	Ser	Leu	Gly	Ile	Val	Phe	Gly
				425					430					435
Pro	Thr	Leu	Leu	Arg	Ala	Glu	Asn	Glu	Thr	Gly	Asn	Met	Ala	Ile
				440					445					450
His	Met	Val	Tyr	Gln	Asn	Gln	Ile	Ala	Glu	Leu	Met	Leu	Ser	Glu
				455					460					465
Tyr	Ser	Lys	Ile	Phe	Gly	Ser	Glu	Glu	Asp					
				470					475					

<210> 20

<211> 368

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 129023CD1

<400> 20

Met	Ala	Asn	Glu	Asn	His	Gly	Ser	Pro	Arg	Glu	Glu	Ala	Ser	Leu
1				5					10					15
Leu	Ser	His	Ser	Pro	Gly	Thr	Ser	Asn	Gln	Ser	Gln	Pro	Cys	Ser
				20					25					30
Pro	Lys	Pro	Ile	Arg	Leu	Val	Gln	Asp	Leu	Pro	Glu	Glu	Leu	Val
				35					40					45
His	Ala	Gly	Trp	Glu	Lys	Cys	Trp	Ser	Arg	Arg	Glu	Asn	Arg	Pro
				50					55					60
Tyr	Tyr	Phe	Asn	Arg	Phe	Thr	Asn	Gln	Ser	Leu	Trp	Glu	Met	Pro
				65					70					75
Val	Leu	Gly	Gln	His	Asp	Val	Ile	Ser	Asp	Pro	Leu	Gly	Leu	Asn
				80					85					90
Ala	Thr	Pro	Leu	Pro	Gln	Asp	Ser	Ser	Leu	Val	Glu	Thr	Pro	Pro
				95					100					105
Ala	Glu	Asn	Lys	Pro	Arg	Lys	Arg	Gln	Leu	Ser	Glu	Glu	Gln	Pro
				110					115					120
Ser	Gly	Asn	Gly	Val	Lys	Lys	Pro	Lys	Ile	Glu	Ile	Pro	Val	Thr
				125					130					135
Pro	Thr	Gly	Gln	Ser	Val	Pro	Ser	Ser	Pro	Ser	Ile	Pro	Gly	Thr
				140					145					150
Pro	Thr	Leu	Lys	Met	Trp	Gly	Thr	Ser	Pro	Glu	Asp	Lys	Gln	Gln
				155					160					165
Ala	Ala	Leu	Leu	Arg	Pro	Thr	Glu	Val	Tyr	Trp	Asp	Leu	Asp	Ile
				170					175					180
Gln	Thr	Asn	Ala	Val	Ile	Lys	His	Arg	Gly	Pro	Ser	Glu	Val	Leu
				185					190					195
Pro	Pro	His	Pro	Glu	Val	Glu	Leu	Leu	Arg	Ser	Gln	Leu	Ile	Leu
				200					205					210
Lys	Leu	Arg	Gln	His	Tyr	Arg	Glu	Leu	Cys	Gln	Gln	Arg	Glu	Gly
				215					220					225
Ile	Glu	Pro	Pro	Arg	Glu	Ser	Phe	Asn	Arg	Trp	Met	Leu	Glu	Arg
				230					235					240
Lys	Val	Val	Asp	Lys	Gly	Ser	Asp	Pro	Leu	Leu	Pro	Ser	Asn	Cys
				245					250					255
Glu	Pro	Val	Val	Ser	Pro	Ser	Met	Phe	Arg	Glu	Ile	Met	Asn	Asp
				260					265					270
Ile	Pro	Ile	Arg	Leu	Ser	Arg	Ile	Lys	Phe	Arg	Glu	Glu	Ala	Lys
				275					280					285
Arg	Leu	Leu	Phe	Lys	Tyr	Ala	Glu	Ala	Ala	Arg	Arg	Leu	Ile	Glu
				290					295					300

	350		355		360									
Phe	Gln	Glu	Val	Glu	Asn	Phe	Phe	Thr	Phe	Leu	Lys	Asn	Ile	Asn
	365				375									
Asp	Val	Asp	Thr	Ala	Leu	Ser	Phe	Tyr	His	Met	Ala	Gly	Ala	Ser
	380				385									390
Leu	Asp	Lys	Val	Thr	Met	Gln	Gln	Val	Ala	Arg	Thr	Val	Ala	Lys
	395				400									405
Val	Glu	Leu	Ser	Asp	His	Val	Cys	Asp	Val	Val	Phe	Ala	Leu	Phe
	410				415									420
Asp	Cys	Asp	Gly	Asn	Gly	Glu	Leu	Ser	Asn	Lys	Glu	Phe	Val	Ser
	425				430									435
Ile	Met	Lys	Gln	Arg	Leu	Met	Arg	Gly	Leu	Glu	Lys	Pro	Lys	Asp
	440				445									450
Met	Gly	Phe	Thr	Arg	Leu	Met	Gln	Ala	Met	Trp	Lys	Cys	Ala	Gln
	455				460									465
Glu	Thr	Ala	Trp	Asp	Phe	Ala	Leu	Pro	Lys	Gln				
	470								475					

<210> 22

<211> 171

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1682320CD1

<400> 22

Met	Glu	Lys	Arg	Leu	Gln	Glu	Ala	Gln	Leu	Tyr	Lys	Glu	Glu	Gly
1				5					10					15
Asn	Gln	Arg	Tyr	Arg	Glu	Gly	Lys	Tyr	Arg	Asp	Ala	Val	Ser	Arg
				20					25					30
Tyr	His	Arg	Ala	Leu	Leu	Gln	Leu	Arg	Gly	Leu	Asp	Pro	Ser	Leu
				35					40					45
Pro	Ser	Pro	Leu	Pro	Asn	Leu	Gly	Pro	Gln	Gly	Pro	Ala	Leu	Thr
				50					55					60
Pro	Glu	Gln	Glu	Asn	Ile	Leu	His	Thr	Thr	Gln	Thr	Asp	Cys	Tyr
				65					70					75
Asn	Asn	Leu	Ala	Ala	Cys	Leu	Leu	Gln	Met	Glu	Pro	Val	Asn	Tyr
				80					85					90
Glu	Arg	Val	Arg	Glu	Tyr	Ser	Gln	Lys	Val	Leu	Glu	Arg	Gln	Pro
				95					100					105
Asp	Asn	Ala	Lys	Ala	Leu	Tyr	Arg	Ala	Gly	Val	Ala	Phe	Phe	His
				110					115					120
Leu	Gln	Asp	Tyr	Asp	Gln	Ala	Arg	His	Tyr	Leu	Leu	Ala	Ala	Val
				125					130					135
Asn	Arg	Gln	Pro	Lys	Asp	Ala	Asn	Val	Arg	Arg	Tyr	Leu	Gln	Leu
				140					145					150
Thr	Gln	Ser	Glu	Leu	Ser	Ser	Tyr	His	Arg	Lys	Glu	Lys	Gln	Leu
				155					160					165
Tyr	Leu	Gly	Met	Phe	Gly									
				170										

<210> 23

<211> 163

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1728263CD1

<400> 23

Met	Phe	Phe	Ser	Glu	Ala	Arg	Ala	Arg	Ser	Arg	Thr	Trp	Glu	Ala
1				5					10					15
Ser	Pro	Ser	Glu	His	Arg	Lys	Trp	Val	Glu	Val	Phe	Lys	Ala	Cys
				20					25					30
Asp	Glu	Asp	His	Lys	Gly	Tyr	Leu	Ser	Arg	Glu	Asp	Phe	Lys	Thr
				35					40					45

Ala	Val	Val	Met	Leu	Phe	Gly	Tyr	Lys	Pro	Ser	Lys	Ile	Glu	Val
				50					55					60
Asp	Ser	Val	Met	Ser	Ser	Ile	Asn	Pro	Asn	Thr	Ser	Gly	Ile	Leu
				65					70					75
Leu	Glu	Gly	Phe	Leu	Asn	Ile	Val	Arg	Lys	Lys	Lys	Glu	Ala	Gln
				80					85					90
Arg	Tyr	Arg	Asn	Glu	Val	Arg	His	Ile	Phe	Thr	Ala	Phe	Asp	Thr
				95					100					105
Tyr	Tyr	Arg	Gly	Phe	Leu	Thr	Leu	Glu	Asp	Phe	Lys	Lys	Ala	Phe
				110					115					120
Arg	Gln	Val	Ala	Pro	Lys	Leu	Pro	Glu	Arg	Thr	Val	Leu	Glu	Val
				125					130					135
Phe	Arg	Glu	Val	Asp	Arg	Asp	Ser	Asp	Gly	His	Val	Ser	Phe	Arg
				140					145					150
Asp	Phe	Glu	Tyr	Ala	Leu	Asn	Tyr	Gly	Gln	Lys	Glu	Ala		
				155					160					

<210> 24

<211> 354

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1867626CD1

<400> 24

Met	Gly	Glu	Gln	Pro	Ile	Phe	Ser	Thr	Arg	Ala	His	Val	Phe	Gln
1				5					10					15
Ile	Asp	Pro	Asn	Thr	Lys	Lys	Asn	Trp	Val	Pro	Thr	Ser	Lys	His
				20					25					30
Ala	Val	Thr	Val	Ser	Tyr	Phe	Tyr	Asp	Ser	Thr	Arg	Asn	Val	Tyr
				35					40					45
Arg	Ile	Ile	Ser	Leu	Asp	Gly	Ser	Lys	Ala	Ile	Ile	Asn	Ser	Thr
				50					55					60
Ile	Thr	Pro	Asn	Met	Thr	Phe	Thr	Lys	Thr	Ser	Gln	Arg	Phe	Gly
				65					70					75
Gln	Trp	Ala	Asp	Ser	Arg	Ala	Asn	Thr	Val	Tyr	Gly	Leu	Gly	Phe
				80					85					90
Ser	Ser	Glu	His	His	Leu	Ser	Lys	Phe	Ala	Glu	Lys	Phe	Gln	Glu
				95					100					105
Phe	Lys	Glu	Ala	Ala	Arg	Leu	Ala	Lys	Glu	Lys	Ser	Gln	Glu	Lys
				110					115					120
Met	Glu	Leu	Thr	Ser	Thr	Pro	Ser	Gln	Glu	Ser	Ala	Gly	Gly	Asp
				125					130					135
Leu	Gln	Ser	Pro	Leu	Thr	Pro	Glu	Ser	Ile	Asn	Gly	Thr	Asp	Asp
				140					145					150
Glu	Arg	Thr	Pro	Asp	Val	Thr	Gln	Asn	Ser	Glu	Pro	Arg	Ala	Glu
				155					160					165
Pro	Thr	Gln	Asn	Ala	Leu	Pro	Phe	Ser	His	Ser	Ser	Ala	Ile	Ser
				170					175					180
Lys	His	Trp	Glu	Ala	Glu	Leu	Ala	Thr	Leu	Lys	Gly	Asn	Asn	Ala
				185					190					195
Lys	Leu	Thr	Ala	Ala	Leu	Leu	Glu	Ser	Thr	Ala	Asn	Val	Lys	Gln
				200					205					210
Trp	Lys	Gln	Gln	Leu	Ala	Ala	Tyr	Gln	Glu	Glu	Ala	Glu	Arg	Leu
				215					220					225
His	Lys	Arg	Val	Thr	Glu	Leu	Glu	Cys	Val	Ser	Ser	Gln	Ala	Asn
				230					235					240
Ala	Val	His	Thr	His	Lys	Thr	Glu	Leu	Asn	Gln	Thr	Ile	Gln	Glu
				245					250					255
Leu	Glu	Glu	Thr	Leu	Lys	Leu	Lys	Glu	Glu	Glu	Ile	Glu	Arg	Leu
				260					265					270
Lys	Gln	Glu	Ile	Asp	Asn	Ala	Arg	Glu	Leu	Gln	Glu	Gln	Arg	Asp
				275					280					285
Ser	Leu	Thr	Gln	Lys	Leu	Gln	Glu	Val	Glu	Ile	Arg	Asn	Lys	Asp
				290					295					300
Leu	Glu	Gly	Gln	Leu	Ser	Asp	Leu	Glu	Gln	Arg	Leu	Glu	Lys	Ser

	305		310		315
Gln Asn Glu Gln	Glu Ala Phe Arg Asn	Asn Leu Lys Thr Leu	Leu		
	320		325		330
Glu Ile Leu Asp	Gly Lys Ile Phe Glu	Leu Thr Glu Leu Arg	Asp		
	335		340		345
Asn Leu Ala Lys	Leu Leu Glu Cys Ser				
	350				

<210> 25

<211> 365

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1990126CD1

<400> 25

Met Asn Ile Met Asp	Phe Asn Val Lys Lys	Leu Ala Ala Asp	Ala
1	5	10	15
Gly Thr Phe Leu Ser	Arg Ala Val Gln Phe	Thr Glu Glu Lys	Leu
	20	25	30
Gly Gln Ala Glu Lys	Thr Glu Leu Asp Ala	His Leu Glu Asn	Leu
	35	40	45
Leu Ser Lys Ala Glu	Cys Thr Lys Ile Trp	Thr Glu Lys Ile	Met
	50	55	60
Lys Gln Thr Glu Val	Leu Leu Gln Pro Asn	Pro Asn Ala Arg	Ile
	65	70	75
Glu Glu Phe Val Tyr	Glu Lys Leu Asp Arg	Lys Ala Pro Ser	Arg
	80	85	90
Ile Asn Asn Pro Glu	Leu Leu Gly Gln Tyr	Met Ile Asp Ala	Gly
	95	100	105
Thr Glu Phe Gly Pro	Gly Thr Ala Tyr Gly	Asn Ala Leu Ile	Lys
	110	115	120
Cys Gly Glu Thr Gln	Lys Arg Ile Gly Thr	Ala Asp Arg Glu	Leu
	125	130	135
Ile Gln Thr Ser Ala	Leu Asn Phe Leu Thr	Pro Leu Arg Asn	Phe
	140	145	150
Ile Glu Gly Asp Tyr	Lys Thr Ile Ala Lys	Glu Arg Lys Leu	Leu
	155	160	165
Gln Asn Lys Arg Leu	Asp Leu Asp Ala Ala	Lys Thr Arg Leu	Lys
	170	175	180
Lys Ala Lys Ala Ala	Glu Thr Arg Asn Ser	Ser Glu Gln Glu	Leu
	185	190	195
Arg Ile Thr Gln Ser	Glu Phe Asp Arg Gln	Ala Glu Ile Thr	Arg
	200	205	210
Leu Leu Leu Glu Gly	Ile Ser Ser Thr His	Ala His His Leu	Arg
	215	220	225
Cys Leu Asn Asp Phe	Val Glu Ala Gln Met	Thr Tyr Tyr Ala	Gln
	230	235	240
Cys Tyr Gln Tyr Met	Leu Asp Leu Gln Lys	Gln Leu Gly Ser	Phe
	245	250	255
Pro Ser Asn Tyr Leu	Ser Asn Asn Asn Gln	Thr Ser Val Thr	Pro
	260	265	270
Val Pro Ser Val Leu	Pro Asn Ala Ile Gly	Ser Ser Ala Met	Ala
	275	280	285
Ser Thr Ser Gly Leu	Val Ile Thr Ser Pro	Ser Asn Leu Ser	Asp
	290	295	300
Leu Lys Glu Cys Ser	Gly Ser Arg Lys Ala	Arg Val Leu Tyr	Asp
	305	310	315
Tyr Asp Ala Ala Asn	Ser Thr Glu Leu Ser	Leu Leu Ala Asp	Glu
	320	325	330
Val Ile Thr Val Phe	Ser Val Val Gly Met	Asp Ser Asp Trp	Leu
	335	340	345
Met Gly Glu Arg Gly	Asn Gln Lys Gly Lys	Val Pro Ile Thr	Tyr
	350	355	360
Leu Glu Leu Leu Asn			
	365		

<210> 26
 <211> 274
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2104180CD1

<400> 26
 Met Ala Thr Thr Val Ser Thr Gln Arg Gly Pro Val Tyr Ile Gly
 1 5 10 15
 Glu Leu Pro Gln Asp Phe Leu Arg Ile Thr Pro Thr Gln Gln Gln
 20 25 30
 Arg Gln Val Gln Leu Asp Ala Gln Ala Ala Gln Gln Leu Gln Tyr
 35 40 45
 Gly Gly Ala Val Gly Thr Val Gly Arg Leu Asn Ile Thr Val Val
 50 55 60
 Gln Ala Lys Leu Ala Lys Asn Tyr Gly Met Thr Arg Met Asp Pro
 65 70 75
 Tyr Cys Arg Leu Arg Leu Gly Tyr Ala Val Tyr Glu Thr Pro Thr
 80 85 90
 Ala His Asn Gly Ala Lys Asn Pro Arg Trp Asn Lys Val Ile His
 95 100 105
 Cys Thr Val Pro Pro Gly Val Asp Ser Phe Tyr Leu Glu Ile Phe
 110 115 120
 Asp Glu Arg Ala Phe Ser Met Asp Asp Arg Ile Ala Trp Thr His
 125 130 135
 Ile Thr Ile Pro Glu Ser Leu Arg Gln Gly Lys Val Glu Asp Lys
 140 145 150
 Trp Tyr Ser Leu Ser Gly Arg Gln Gly Asp Asp Lys Glu Gly Met
 155 160 165
 Ile Asn Leu Val Met Ser Tyr Ala Leu Leu Pro Ala Ala Met Val
 170 175 180
 Met Pro Pro Gln Pro Val Val Leu Met Pro Thr Val Tyr Gln Gln
 185 190 195
 Gly Val Gly Tyr Val Pro Ile Thr Gly Met Pro Ala Val Cys Ser
 200 205 210
 Pro Gly Met Val Pro Val Ala Leu Pro Pro Ala Ala Val Asn Ala
 215 220 225
 Gln Pro Arg Cys Ser Glu Glu Asp Leu Lys Ala Ile Gln Asp Met
 230 235 240
 Phe Pro Asn Met Asp Gln Glu Val Ile Arg Ser Val Leu Glu Ala
 245 250 255
 Gln Arg Gly Asn Lys Asp Ala Ala Ile Asn Ser Leu Leu Gln Met
 260 265 270
 Gly Glu Glu Pro

<210> 27
 <211> 129
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2122241CD1

<400> 27
 Met Arg Arg Arg Gly Glu Ile Asp Met Ala Thr Glu Gly Asp Val
 1 5 10 15
 Glu Leu Glu Leu Glu Thr Glu Thr Ser Gly Pro Glu Arg Pro Pro
 20 25 30
 Glu Lys Pro Arg Lys His Asp Ser Gly Ala Ala Asp Leu Glu Arg
 35 40 45
 Val Thr Asp Tyr Ala Glu Glu Lys Glu Ile Gln Ser Ser Asn Leu
 50 55 60
 Glu Thr Ala Met Ser Val Ile Gly Asp Arg Arg Ser Arg Glu Gln

				65					70					75
Lys	Ala	Lys	Gln	Glu	Arg	Glu	Lys	Glu	Leu	Ala	Lys	Val	Thr	Ile
				80					85					90
Lys	Lys	Glu	Asp	Leu	Glu	Leu	Ile	Met	Thr	Glu	Met	Glu	Ile	Ser
				95					100					105
Arg	Ala	Ala	Ala	Glu	Arg	Ser	Leu	Arg	Glu	His	Met	Gly	Asn	Val
				110					115					120
Val	Glu	Ala	Leu	Ile	Ala	Leu	Thr	Asn						
				125										

<210> 28

<211> 626

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2580428CD1

<400> 28

Met	Gln	Arg	Ala	Asp	Ser	Glu	Gln	Pro	Ser	Lys	Arg	Pro	Arg	Cys
1				5					10					15
Asp	Asp	Ser	Pro	Arg	Thr	Pro	Ser	Asn	Thr	Pro	Ser	Ala	Glu	Ala
				20					25					30
Asp	Trp	Ser	Pro	Gly	Leu	Glu	Leu	His	Pro	Asp	Tyr	Lys	Thr	Trp
				35					40					45
Gly	Pro	Glu	Gln	Val	Cys	Ser	Phe	Leu	Arg	Arg	Gly	Gly	Phe	Glu
				50					55					60
Glu	Pro	Val	Leu	Leu	Lys	Asn	Ile	Arg	Glu	Asn	Glu	Ile	Thr	Gly
				65					70					75
Ala	Leu	Leu	Pro	Cys	Leu	Asp	Glu	Ser	Arg	Phe	Glu	Asn	Leu	Gly
				80					85					90
Val	Ser	Ser	Leu	Gly	Glu	Arg	Lys	Lys	Leu	Leu	Ser	Tyr	Ile	Gln
				95					100					105
Arg	Leu	Val	Gln	Ile	His	Val	Asp	Thr	Met	Lys	Val	Ile	Asn	Asp
				110					115					120
Pro	Ile	His	Gly	His	Ile	Glu	Leu	His	Pro	Leu	Leu	Val	Arg	Ile
				125					130					135
Ile	Asp	Thr	Pro	Gln	Phe	Gln	Arg	Leu	Arg	Tyr	Ile	Lys	Gln	Leu
				140					145					150
Gly	Gly	Gly	Tyr	Tyr	Val	Phe	Pro	Gly	Ala	Ser	His	Asn	Arg	Phe
				155					160					165
Glu	His	Ser	Leu	Gly	Val	Gly	Tyr	Leu	Ala	Gly	Cys	Leu	Val	His
				170					175					180
Ala	Leu	Gly	Glu	Lys	Gln	Pro	Glu	Leu	Gln	Ile	Ser	Glu	Arg	Asp
				185					190					195
Val	Leu	Cys	Val	Gln	Ile	Ala	Gly	Leu	Cys	His	Asp	Leu	Gly	His
				200					205					210
Gly	Pro	Phe	Ser	His	Met	Phe	Asp	Gly	Arg	Phe	Ile	Pro	Leu	Ala
				215					220					225
Arg	Pro	Glu	Val	Lys	Trp	Thr	His	Glu	Gln	Gly	Ser	Val	Met	Met
				230					235					240
Phe	Glu	His	Leu	Ile	Asn	Ser	Asn	Gly	Ile	Lys	Pro	Val	Met	Glu
				245					250					255
Gln	Tyr	Gly	Leu	Ile	Pro	Glu	Glu	Asp	Ile	Cys	Phe	Ile	Lys	Glu
				260					265					270
Gln	Ile	Val	Gly	Pro	Leu	Glu	Ser	Pro	Val	Glu	Asp	Ser	Leu	Trp
				275					280					285
Pro	Tyr	Lys	Gly	Arg	Pro	Glu	Asn	Lys	Ser	Phe	Leu	Tyr	Glu	Ile
				290					295					300
Val	Ser	Asn	Lys	Arg	Asn	Gly	Ile	Asp	Val	Asp	Lys	Trp	Asp	Tyr
				305					310					315
Phe	Ala	Arg	Asp	Cys	His	His	Leu	Gly	Ile	Gln	Asn	Asn	Phe	Asp
				320					325					330
Tyr	Lys	Arg	Phe	Ile	Lys	Phe	Ala	Arg	Val	Cys	Glu	Val	Asp	Asn
				335					340					345
Glu	Leu	Arg	Ile	Cys	Ala	Arg	Asp	Lys	Glu	Val	Gly	Asn	Leu	Tyr
				350					355					360

Asp	Met	Phe	His	Thr	Arg	Asn	Ser	Leu	His	Arg	Arg	Ala	Tyr	Gln
				365					370					375
His	Lys	Val	Gly	Asn	Ile	Ile	Asp	Thr	Met	Ile	Thr	Asp	Ala	Phe
				380					385					390
Leu	Lys	Ala	Asp	Asp	Tyr	Ile	Glu	Ile	Thr	Gly	Ala	Gly	Gly	Lys
				395					400					405
Lys	Tyr	Arg	Ile	Ser	Thr	Ala	Ile	Asp	Asp	Met	Glu	Ala	Tyr	Thr
				410					415					420
Lys	Leu	Thr	Asp	Asn	Ile	Phe	Leu	Glu	Ile	Leu	Tyr	Ser	Thr	Asp
				425					430					435
Pro	Lys	Leu	Lys	Asp	Ala	Arg	Glu	Ile	Leu	Lys	Gln	Ile	Glu	Tyr
				440					445					450
Arg	Asn	Leu	Phe	Lys	Tyr	Val	Gly	Glu	Thr	Gln	Pro	Thr	Gly	Gln
				455					460					465
Ile	Lys	Ile	Lys	Arg	Glu	Asp	Tyr	Glu	Ser	Leu	Pro	Lys	Glu	Val
				470					475					480
Ala	Ser	Ala	Lys	Pro	Lys	Val	Leu	Leu	Asp	Val	Lys	Leu	Lys	Ala
				485					490					495
Glu	Asp	Phe	Ile	Val	Asp	Val	Ile	Asn	Met	Asp	Tyr	Gly	Met	Gln
				500					505					510
Glu	Lys	Asn	Pro	Ile	Asp	His	Val	Ser	Phe	Tyr	Cys	Lys	Thr	Ala
				515					520					525
Pro	Asn	Arg	Ala	Ile	Arg	Ile	Thr	Lys	Asn	Gln	Val	Ser	Gln	Leu
				530					535					540
Leu	Pro	Glu	Lys	Phe	Ala	Glu	Gln	Leu	Ile	Arg	Val	Tyr	Cys	Lys
				545					550					555
Lys	Val	Asp	Arg	Lys	Ser	Leu	Tyr	Ala	Ala	Arg	Gln	Tyr	Phe	Val
				560					565					570
Gln	Trp	Cys	Ala	Asp	Arg	Asn	Phe	Thr	Lys	Pro	Gln	Asp	Gly	Asp
				575					580					585
Val	Ile	Ala	Pro	Leu	Ile	Thr	Pro	Gln	Lys	Lys	Glu	Trp	Asn	Asp
				590					595					600
Ser	Thr	Ser	Val	Gln	Asn	Pro	Thr	Arg	Leu	Arg	Glu	Ala	Ser	Lys
				605					610					615
Ser	Arg	Val	Gln	Leu	Phe	Lys	Asp	Asp	Pro	Met				
				620					625					

<210> 29

<211> 157

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3397189CD1

<400> 29

Met	Ala	Pro	Lys	Lys	Leu	Ser	Cys	Leu	Arg	Ser	Leu	Leu	Leu	Pro
1				5					10					15
Leu	Ser	Leu	Thr	Leu	Leu	Leu	Pro	Gln	Ala	Asp	Thr	Arg	Ser	Phe
				20					25					30
Val	Val	Asp	Arg	Gly	His	Asp	Arg	Phe	Leu	Leu	Asp	Gly	Ala	Pro
				35					40					45
Phe	Arg	Tyr	Val	Ser	Gly	Ser	Leu	His	Tyr	Phe	Arg	Val	Pro	Arg
				50					55					60
Val	Leu	Trp	Ala	Asp	Arg	Leu	Leu	Lys	Met	Arg	Trp	Ser	Gly	Leu
				65					70					75
Asn	Ala	Ile	Gln	Phe	Tyr	Val	Pro	Trp	Asn	Tyr	His	Glu	Pro	Gln
				80					85					90
Pro	Gly	Val	Tyr	Asn	Phe	Asn	Gly	Ser	Arg	Asp	Leu	Ile	Ala	Phe
				95					100					105
Leu	Asn	Glu	Ala	Ala	Leu	Ala	Asn	Leu	Leu	Val	Ile	Leu	Arg	Pro
				110					115					120
Gly	Pro	Tyr	Ile	Cys	Ala	Glu	Trp	Glu	Met	Gly	Gly	Leu	Pro	Ser
				125					130					135
Trp	Leu	Leu	Arg	Lys	Pro	Glu	Ile	His	Leu	Arg	Thr	Ser	Asp	Pro
				140					145					150
Gly	Glu	Leu	Arg	Gln	Arg	Ile								

155

<210> 30
 <211> 383
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 4881249CD1

<400> 30

Met	Leu	Ser	Arg	Lys	Lys	Thr	Lys	Asn	Glu	Val	Ser	Lys	Pro	Ala
1				5					10					15
Glu	Val	Gln	Gly	Lys	Tyr	Val	Lys	Lys	Glu	Thr	Ser	Pro	Leu	Leu
				20					25					30
Arg	Asn	Leu	Met	Pro	Ser	Phe	Ile	Arg	His	Gly	Pro	Thr	Ile	Pro
				35					40					45
Arg	Arg	Thr	Asp	Ile	Cys	Leu	Pro	Asp	Ser	Ser	Pro	Asn	Ala	Phe
				50					55					60
Ser	Thr	Ser	Gly	Asp	Val	Val	Ser	Arg	Asn	Gln	Ser	Phe	Leu	Arg
				65					70					75
Thr	Pro	Ile	Gln	Arg	Thr	Pro	His	Glu	Ile	Met	Arg	Arg	Glu	Ser
				80					85					90
Asn	Arg	Leu	Ser	Ala	Pro	Ser	Tyr	Leu	Ala	Arg	Ser	Leu	Ala	Asp
				95					100					105
Val	Pro	Arg	Glu	Tyr	Gly	Ser	Ser	Gln	Ser	Phe	Val	Thr	Glu	Val
				110					115					120
Ser	Phe	Ala	Val	Glu	Asn	Gly	Asp	Ser	Gly	Ser	Arg	Tyr	Tyr	Tyr
				125					130					135
Ser	Asp	Asn	Phe	Phe	Asp	Gly	Gln	Arg	Lys	Arg	Pro	Leu	Gly	Asp
				140					145					150
Arg	Ala	His	Glu	Asp	Tyr	Arg	Tyr	Tyr	Glu	Tyr	Asn	His	Asp	Leu
				155					160					165
Phe	Gln	Arg	Met	Pro	Gln	Asn	Gln	Gly	Arg	His	Ala	Ser	Gly	Ile
				170					175					180
Gly	Arg	Val	Ala	Ala	Thr	Ser	Leu	Gly	Asn	Leu	Thr	Asn	His	Gly
				185					190					195
Ser	Glu	Asp	Leu	Pro	Leu	Pro	Pro	Gly	Trp	Ser	Val	Asp	Trp	Thr
				200					205					210
Met	Arg	Gly	Arg	Lys	Tyr	Tyr	Ile	Asp	His	Asn	Thr	Asn	Thr	Thr
				215					220					225
His	Trp	Ser	His	Pro	Leu	Glu	Arg	Glu	Gly	Leu	Pro	Pro	Gly	Trp
				230					235					240
Glu	Arg	Val	Glu	Ser	Ser	Glu	Phe	Gly	Thr	Tyr	Tyr	Val	Asp	His
				245					250					255
Thr	Asn	Lys	Lys	Ala	Gln	Tyr	Arg	His	Pro	Cys	Ala	Pro	Ser	Val
				260					265					270
Pro	Arg	Tyr	Asp	Gln	Pro	Pro	Pro	Val	Thr	Tyr	Gln	Pro	Gln	Gln
				275					280					285
Thr	Glu	Arg	Asn	Gln	Ser	Leu	Leu	Val	Pro	Ala	Asn	Pro	Tyr	His
				290					295					300
Thr	Ala	Glu	Ile	Pro	Asp	Trp	Leu	Gln	Val	Tyr	Ala	Arg	Ala	Pro
				305					310					315
Val	Lys	Tyr	Asp	His	Ile	Leu	Lys	Trp	Glu	Leu	Phe	Gln	Leu	Ala
				320					325					330
Asp	Leu	Asp	Thr	Tyr	Gln	Gly	Met	Leu	Lys	Leu	Leu	Phe	Met	Lys
				335					340					345
Glu	Leu	Glu	Gln	Ile	Val	Lys	Met	Tyr	Glu	Ala	Tyr	Arg	Gln	Ala
				350					355					360
Leu	Leu	Thr	Glu	Leu	Glu	Asn	Arg	Lys	Gln	Arg	Gln	Gln	Trp	Tyr
				365					370					375
Ala	Gln	Gln	His	Gly	Lys	Asn	Phe							
				380										

<210> 31
 <211> 478
 <212> PRT
 <213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 431871CD1

<400> 31

Met	Asp	Thr	Ser	Asp	Leu	Phe	Ala	Ser	Cys	Arg	Lys	Gly	Asp	Val
1				5					10					15
Gly	Arg	Val	Arg	Tyr	Leu	Leu	Glu	Gln	Arg	Asp	Val	Glu	Val	Asn
				20					25					30
Val	Arg	Asp	Lys	Trp	Asp	Ser	Thr	Pro	Leu	Tyr	Tyr	Ala	Cys	Leu
				35					40					45
Cys	Gly	His	Glu	Glu	Leu	Val	Leu	Tyr	Leu	Leu	Ala	Asn	Gly	Ala
				50					55					60
Arg	Cys	Glu	Ala	Asn	Thr	Phe	Asp	Gly	Glu	Arg	Cys	Leu	Tyr	Gly
				65					70					75
Ala	Leu	Ser	Asp	Pro	Ile	Arg	Arg	Ala	Leu	Arg	Asp	Tyr	Lys	Gln
				80					85					90
Val	Thr	Ala	Ser	Cys	Arg	Arg	Arg	Asp	Tyr	Tyr	Asp	Asp	Phe	Leu
				95					100					105
Gln	Arg	Leu	Leu	Glu	Gln	Gly	Ile	His	Ser	Asp	Val	Val	Phe	Val
				110					115					120
Val	His	Gly	Lys	Pro	Phe	Arg	Val	His	Arg	Cys	Val	Leu	Gly	Ala
				125					130					135
Arg	Ser	Ala	Tyr	Phe	Ala	Asn	Met	Leu	Asp	Thr	Lys	Trp	Lys	Gly
				140					145					150
Lys	Ser	Val	Val	Val	Leu	Arg	His	Pro	Leu	Ile	Asn	Pro	Val	Ala
				155					160					165
Phe	Gly	Ala	Leu	Leu	Gln	Tyr	Leu	Tyr	Thr	Gly	Arg	Leu	Asp	Ile
				170					175					180
Gly	Val	Glu	His	Val	Ser	Asp	Cys	Glu	Arg	Leu	Ala	Lys	Gln	Cys
				185					190					195
Gln	Leu	Trp	Asp	Leu	Leu	Ser	Asp	Leu	Glu	Ala	Lys	Cys	Glu	Lys
				200					205					210
Val	Ser	Glu	Phe	Val	Ala	Ser	Lys	Pro	Gly	Thr	Cys	Val	Lys	Val
				215					220					225
Leu	Thr	Ile	Glu	Pro	Pro	Pro	Ala	Asp	Pro	Arg	Leu	Arg	Glu	Asp
				230					235					240
Met	Ala	Leu	Leu	Ala	Asp	Cys	Ala	Leu	Pro	Pro	Glu	Leu	Arg	Gly
				245					250					255
Asp	Leu	Trp	Glu	Leu	Pro	Phe	Pro	Cys	Pro	Asp	Gly	Phe	Asn	Ser
				260					265					270
Cys	Pro	Asp	Ile	Cys	Phe	Arg	Val	Ala	Gly	Cys	Ser	Phe	Leu	Cys
				275					280					285
His	Lys	Ala	Phe	Phe	Cys	Gly	Arg	Ser	Asp	Tyr	Phe	Arg	Ala	Leu
				290					295					300
Leu	Asp	Asp	His	Phe	Arg	Glu	Ser	Glu	Glu	Pro	Ala	Thr	Ser	Gly
				305					310					315
Gly	Pro	Pro	Ala	Val	Thr	Leu	His	Gly	Ile	Ser	Pro	Asp	Val	Phe
				320					325					330
Thr	His	Val	Leu	Tyr	Tyr	Met	Tyr	Ser	Asp	His	Thr	Glu	Leu	Ser
				335					340					345
Pro	Glu	Ala	Ala	Tyr	Asp	Val	Leu	Ser	Val	Ala	Asp	Met	Tyr	Leu
				350					355					360
Leu	Pro	Gly	Leu	Lys	Arg	Leu	Cys	Gly	Arg	Ser	Leu	Ala	Gln	Met
				365					370					375
Leu	Asp	Glu	Asp	Thr	Val	Val	Gly	Val	Trp	Arg	Val	Ala	Lys	Leu
				380					385					390
Phe	Arg	Leu	Ala	Arg	Leu	Glu	Asp	Gln	Cys	Thr	Glu	Tyr	Met	Ala
				395					400					405
Lys	Val	Ile	Glu	Lys	Leu	Val	Glu	Arg	Glu	Asp	Phe	Val	Glu	Ala
				410					415					420
Val	Lys	Glu	Glu	Ala	Ala	Ala	Val	Ala	Ala	Arg	Gln	Glu	Thr	Asp
				425					430					435
Ser	Ile	Pro	Leu	Val	Asp	Asp	Ile	Arg	Phe	His	Val	Ala	Ser	Thr
				440					445					450
Val	Gln	Thr	Tyr	Ser	Ala	Ile	Glu	Glu	Ala	Gln	Gln	Arg	Leu	Arg
				455					460					465

Ala Leu Glu Asp Leu Leu Val Ser Ile Gly Leu Asp Cys
470 475

<210> 32
<211> 275
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 526155CD1

<400> 32
Met Ser Ala Glu Val Lys Val Thr Gly Gln Asn Gln Glu Gln Phe
1 5 10 15
Leu Leu Leu Ala Lys Ser Ala Lys Gly Ala Ala Leu Ala Thr Leu
20 25 30
Ile His Gln Val Leu Glu Ala Pro Gly Val Tyr Val Phe Gly Glu
35 40 45
Leu Leu Asp Met Pro Asn Val Arg Glu Leu Ala Glu Ser Asp Phe
50 55 60
Ala Ser Thr Phe Arg Leu Leu Thr Val Phe Ala Tyr Gly Thr Tyr
65 70 75
Ala Asp Tyr Leu Ala Glu Ala Arg Asn Leu Pro Pro Leu Thr Glu
80 85 90
Ala Gln Lys Asn Lys Leu Arg His Leu Ser Val Val Thr Leu Ala
95 100 105
Ala Lys Val Lys Cys Ile Pro Tyr Ala Val Leu Leu Glu Ala Leu
110 115 120
Ala Leu Arg Asn Val Arg Gln Leu Glu Asp Leu Val Ile Glu Ala
125 130 135
Val Tyr Ala Asp Val Leu Arg Gly Ser Leu Asp Gln Arg Asn Gln
140 145 150
Arg Leu Glu Val Asp Tyr Ser Ile Gly Arg Asp Ile Gln Arg Gln
155 160 165
Asp Leu Ser Ala Ile Ala Arg Thr Leu Gln Glu Trp Cys Val Gly
170 175 180
Cys Glu Val Val Leu Ser Gly Ile Glu Glu Gln Val Ser Arg Ala
185 190 195
Asn Gln His Lys Glu Gln Gln Leu Gly Leu Lys Gln Gln Ile Glu
200 205 210
Ser Glu Val Ala Asn Leu Lys Lys Thr Ile Lys Val Thr Thr Ala
215 220 225
Ala Ala Ala Ala Ala Thr Ser Gln Asp Pro Glu Gln His Leu Thr
230 235 240
Glu Leu Arg Glu Pro Ala Pro Gly Thr Asn Gln Arg Gln Pro Ser
245 250 255
Lys Lys Ala Ser Lys Gly Lys Gly Leu Arg Gly Ser Ala Lys Ile
260 265 270
Trp Ser Lys Ser Asn
275

<210> 33
<211> 217
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 676234CD1

<400> 33
Met Ala Ser Thr Gly Leu Glu Leu Leu Gly Met Thr Leu Ala Val
1 5 10 15
Leu Gly Trp Leu Gly Thr Leu Val Ser Cys Ala Leu Pro Leu Trp
20 25 30
Lys Val Thr Ala Phe Ile Gly Asn Ser Ile Val Val Ala Gln Val

Val Trp Glu Gly	35	Leu Trp Met Ser Cys	40	Val Val Gln Ser Thr	45
Gln Met Gln Cys	50	Lys Val Tyr Asp Ser	55	Leu Ala Leu Pro	60
Asp Leu Gln Ala	65	Ala Arg Ala Leu Cys	70	Ile Ala Leu Leu	75
Ala Leu Leu Gly	80	Leu Val Ala Ile	85	Thr Gly Ala Gln	90
Thr Cys Val Glu	95	Asp Glu Gly Ala Lys	100	Ala Arg Ile Val	105
Ala Gly Val Ile	110	Leu Leu Leu Ala	115	Gly Ile Leu Val	120
Val Cys Trp Thr	125	Ala His Ala Ile	130	Ile Leu Val Leu	135
Leu Val Ala Glu	140	Ala Leu Lys Arg	145	Gln Asp Phe Tyr	150
Leu Gly Trp Ala	155	Ala Ala Leu Leu	160	Met Gly Ala Ser	165
Leu Cys Cys Thr	170	Cys Pro Pro Pro	175	Gln Val Glu Arg	180
Pro Arg Leu Gly	185	Tyr Ser Ile Pro	190	Ser Gly Ala Ser	195
Leu Asp Lys Arg	200	Asp Tyr Val	205		210
	215				

<210> 34

<211> 74

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 720145CD1

<400> 34

Met Asp Asp Tyr	1	Thr Ser Ala Ile	5	Glu Val Gln Pro	10	Asn Phe Glu	15
Val Pro Tyr Tyr	20	Asn Arg Gly Leu	25	Ile Leu Tyr Arg	30	Leu Gly Tyr	35
Phe Asp Asp Ala	35	Leu Glu Asp Phe	40	Lys Lys Val Leu	45	Asp Leu Asn	50
Pro Gly Phe Gln	50	Asp Ala Thr Leu	55	Ser Leu Lys Gln	60	Thr Ile Leu	65
Asp Lys Glu Glu	65	Lys Gln Arg Arg	70	Asn Val Ala Lys	75	Asn Tyr	80

<210> 35

<211> 367

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1001951CD1

<400> 35

Met Val Gln Gln	1	Phe Leu Arg Gln	5	Ala Gln Arg Gly	10	Thr Glu Glu	15
Lys Glu Arg Glu	20	Gly Ala Leu Val	25	Ser Leu Arg Arg	30	Gly Leu Gln	35
His Pro Glu Thr	35	Gln Gln Thr Phe	40	Ile Arg Ser Cys	45	Val Cys Ile	50
His Trp Val Thr	50	Leu Ile Val Glu	55	Ser Glu Ala Val	60	Arg Arg Gln	65
Leu Leu Pro Gln	65	Gly Ile Val Pro	70	Ala Leu Ala Ala	75	Cys Ile Gln	80
Ser Pro His Val	80	Ala Val Leu Glu	85	Ala Leu Gly Tyr	90	Ala Leu Ser	95

Gln	Leu	Leu	Gln	Ala	Gln	Glu	Ala	Pro	Glu	Lys	Ile	Ile	Pro	Ser
				95					100					105
Ile	Leu	Ala	Ser	Thr	Leu	Pro	Gln	His	Met	Leu	Gln	Met	Leu	Gln
				110					115					120
Pro	Gly	Pro	Lys	Leu	Asn	Pro	Gly	Val	Ala	Val	Glu	Phe	Ala	Trp
				125					130					135
Cys	Leu	His	Tyr	Ile	Ile	Cys	Ser	Gln	Val	Ser	Asn	Pro	Leu	Leu
				140					145					150
Ile	Gly	His	Gly	Ala	Leu	Ser	Thr	Leu	Gly	Leu	Leu	Leu	Leu	Asp
				155					160					165
Leu	Ala	Gly	Ala	Val	Gln	Lys	Thr	Glu	Asp	Ala	Gly	Leu	Glu	Leu
				170					175					180
Leu	Ala	Cys	Pro	Val	Leu	Arg	Cys	Leu	Ser	Asn	Leu	Leu	Thr	Glu
				185					190					195
Ala	Ala	Val	Glu	Thr	Val	Gly	Gly	Gln	Met	Gln	Leu	Arg	Asp	Glu
				200					205					210
Arg	Val	Val	Ala	Ala	Leu	Phe	Ile	Leu	Leu	Gln	Phe	Phe	Phe	Gln
				215					220					225
Lys	Gln	Pro	Ser	Leu	Leu	Pro	Glu	Gly	Leu	Trp	Leu	Leu	Asn	Asn
				230					235					240
Leu	Thr	Ala	Asn	Ser	Pro	Ser	Phe	Cys	Thr	Ser	Leu	Leu	Ser	Leu
				245					250					255
Asp	Leu	Ile	Glu	Pro	Leu	Leu	Gln	Leu	Leu	Pro	Val	Ser	Asn	Val
				260					265					270
Val	Ser	Val	Met	Val	Leu	Thr	Val	Leu	Cys	Asn	Val	Ala	Glu	Lys
				275					280					285
Gly	Pro	Ala	Tyr	Cys	Gln	Arg	Leu	Trp	Pro	Gly	Pro	Leu	Leu	Pro
				290					295					300
Ala	Leu	Leu	His	Thr	Leu	Ala	Phe	Ser	Asp	Thr	Glu	Val	Val	Gly
				305					310					315
Gln	Ser	Leu	Glu	Leu	Leu	His	Leu	Leu	Phe	Leu	Tyr	Gln	Pro	Glu
				320					325					330
Ala	Val	Gln	Val	Phe	Leu	Gln	Gln	Ser	Gly	Leu	Gln	Ala	Trp	Lys
				335					340					345
Arg	His	Gln	Glu	Glu	Ala	Gln	Leu	Gln	Asp	Arg	Val	Tyr	Ala	Leu
				350					355					360
Gln	Gln	Thr	Ala	Leu	Gln	Gly								
				365										

<210> 36

<211> 1113

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1243349CD1

<400> 36

Met	Ile	Ala	Val	Ser	Phe	Lys	Cys	Arg	Cys	Gln	Ile	Leu	Arg	Arg
1				5					10					15
Leu	Thr	Lys	Asp	Glu	Ser	Pro	Tyr	Thr	Lys	Ser	Ala	Ser	Gln	Thr
				20					25					30
Lys	Pro	Pro	Asp	Gly	Ala	Leu	Ala	Val	Arg	Arg	Gln	Ser	Ile	Pro
				35					40					45
Glu	Glu	Phe	Lys	Gly	Ser	Thr	Val	Val	Glu	Leu	Met	Lys	Lys	Glu
				50					55					60
Gly	Thr	Thr	Leu	Gly	Leu	Thr	Val	Ser	Gly	Gly	Ile	Asp	Lys	Asp
				65					70					75
Gly	Lys	Pro	Arg	Val	Ser	Asn	Leu	Arg	Gln	Gly	Gly	Ile	Ala	Ala
				80					85					90
Arg	Ser	Asp	Gln	Leu	Asp	Val	Gly	Asp	Tyr	Ile	Lys	Ala	Val	Asn
				95					100					105
Gly	Ile	Asn	Leu	Ala	Lys	Phe	Arg	His	Asp	Glu	Ile	Ile	Ser	Leu
				110					115					120
Leu	Lys	Asn	Val	Gly	Glu	Arg	Val	Val	Leu	Glu	Val	Glu	Tyr	Glu
				125					130					135
Leu	Pro	Pro	Val	Ser	Val	Gln	Gly	Ser	Ser	Val	Ile	Phe	Arg	Thr

Val Glu Val Thr	140	Leu His Lys Glu Gly	145	Asn Thr Phe Gly Phe	150
Ile Arg Gly Gly	155	Ala His Asp Asp Arg	160	Asn Lys Ser Arg Pro	165
Val Ile Thr Cys	170	Val Arg Pro Gly Gly	175	Pro Ala Asp Arg Glu	180
Thr Ile Lys Pro	185	Gly Asp Arg Leu Leu	190	Val Asp Gly Ile Arg	195
Leu Leu Gly Thr	200	Thr His Ala Glu Ala	205	Met Ser Ile Leu Lys	210
Cys Gly Gln Glu	215	Ala Ala Leu Leu Ile	220	Glu Tyr Asp Val Ser	225
Met Asp Ser Val	230	Ala Thr Ala Ser Gly	235	Pro Leu Leu Val Glu	240
Ala Lys Thr Pro	245	Gly Ala Ser Leu Gly	250	Val Ala Leu Thr Thr	255
Met Cys Cys Asn	260	Lys Gln Val Ile Val	265	Ile Asp Lys Ile Lys	270
Ala Ser Ile Ala	275	Asp Arg Cys Gly Ala	280	Leu His Val Gly Asp	285
Ile Leu Ser Ile	290	Asp Gly Thr Ser Met	295	Glu Tyr Cys Thr Leu	300
Glu Ala Thr Gln	305	Phe Leu Ala Asn Thr	310	Thr Asp Gln Val Lys	315
Glu Ile Leu Pro	320	His His Gln Thr Arg	325	Leu Ala Leu Lys Gly	330
Asp His Val Lys	335	Ile Gln Arg Ser Asp	340	Arg Gln Leu Thr Trp	345
Ser Trp Ala Ser	350	Asn His Ser Ser Leu	355	His Thr Asn His His	360
Asn Thr Tyr His	365	Pro Asp His Cys Arg	370	Val Pro Ala Leu Thr	375
Pro Lys Ala Pro	380	Pro Pro Asn Ser Pro	385	Pro Ala Leu Val Ser	390
Ser Phe Ser Pro	395	Thr Ser Met Ser Ala	400	Ser Leu Ser Ser Ser	405
Asn Met Gly Thr	410	Leu Pro Arg Ser Leu	415	Tyr Ser Thr Ser Pro	420
Gly Thr Met Met	425	Arg Arg Arg Leu Lys	430	Lys Lys Asp Phe Lys	435
Ser Leu Ser Leu	440	Ala Ser Ser Thr Val	445	Gly Leu Ala Gly Gln	450
Val His Thr Glu	455	Thr Thr Glu Val Val	460	Leu Thr Ala Asp Pro	465
Thr Gly Phe Gly	470	Ile Gln Leu Gln Gly	475	Ser Val Phe Ala Thr	480
Thr Leu Ser Ser	485	Pro Pro Leu Ile Ser	490	Tyr Ile Glu Ala Asp	495
Pro Ala Glu Arg	500	Cys Gly Val Leu Gln	505	Ile Gly Asp Arg Val	510
Ala Ile Asn Gly	515	Ile Pro Thr Glu Asp	520	Ser Thr Phe Glu Glu	525
Ser Gln Leu Leu	530	Arg Asp Ser Ser Ile	535	Thr Ser Lys Val Thr	540
Glu Ile Glu Phe	545	Asp Val Ala Glu Ser	550	Val Ile Pro Ser Ser	555
Thr Phe His Val	560	Lys Leu Pro Lys Lys	565	His Asn Val Glu Leu	570
Ile Thr Ile Ser	575	Ser Pro Ser Ser Arg	580	Lys Pro Gly Asp Pro	585
Val Ile Ser Asp	590	Ile Lys Lys Gly Ser	595	Val Ala His Arg Thr	600
Thr Leu Glu Leu	605	Gly Asp Lys Leu Leu	610	Ala Ile Asp Asn Ile	615
Leu Asp Asn Cys	620	Ser Met Glu Asp Ala	625	Val Gln Ile Leu Gln	630
	635		640		645

Cys	Glu	Asp	Leu	Val	Lys	Leu	Lys	Ile	Arg	Lys	Asp	Glu	Asp	Asn
				650					655					660
Ser	Asp	Glu	Gln	Glu	Ser	Ser	Gly	Ala	Ile	Ile	Tyr	Thr	Val	Glu
				665					670					675
Leu	Lys	Arg	Tyr	Gly	Gly	Pro	Leu	Gly	Ile	Thr	Ile	Ser	Gly	Thr
				680					685					690
Glu	Glu	Pro	Phe	Asp	Pro	Ile	Ile	Ile	Ser	Ser	Leu	Thr	Lys	Gly
				695					700					705
Gly	Leu	Ala	Glu	Arg	Thr	Gly	Ala	Ile	His	Ile	Gly	Asp	Arg	Ile
				710					715					720
Leu	Ala	Ile	Asn	Ser	Ser	Ser	Leu	Lys	Gly	Lys	Pro	Leu	Ser	Glu
				725					730					735
Ala	Ile	His	Leu	Leu	Gln	Met	Ala	Gly	Glu	Thr	Val	Thr	Leu	Lys
				740					745					750
Ile	Lys	Lys	Gln	Thr	Asp	Ala	Gln	Ser	Ala	Ser	Ser	Pro	Lys	Lys
				755					760					765
Phe	Pro	Ile	Ser	Ser	His	Leu	Ser	Asp	Leu	Gly	Asp	Val	Glu	Glu
				770					775					780
Asp	Ser	Ser	Pro	Ala	Gln	Lys	Pro	Gly	Lys	Leu	Ser	Asp	Met	Tyr
				785					790					795
Pro	Ser	Thr	Val	Pro	Ser	Val	Asp	Ser	Ala	Val	Asp	Ser	Trp	Asp
				800					805					810
Gly	Ser	Ala	Ile	Asp	Thr	Ser	Tyr	Gly	Thr	Glu	Gly	Thr	Ser	Phe
				815					820					825
Gln	Ala	Ser	Gly	Tyr	Asn	Phe	Asn	Thr	Tyr	Asp	Trp	Arg	Ser	Pro
				830					835					840
Lys	Gln	Arg	Gly	Ser	Leu	Ser	Pro	Val	Thr	Lys	Pro	Arg	Ser	Gln
				845					850					855
Thr	Tyr	Pro	Asp	Val	Gly	Leu	Ser	Tyr	Glu	Asp	Trp	Asp	Arg	Ser
				860					865					870
Thr	Ala	Ser	Gly	Phe	Ala	Gly	Ala	Ala	Asp	Ser	Ala	Glu	Thr	Glu
				875					880					885
Gln	Glu	Glu	Asn	Phe	Trp	Ser	Gln	Ala	Leu	Glu	Asp	Leu	Glu	Thr
				890					895					900
Cys	Gly	Gln	Ser	Gly	Ile	Leu	Arg	Glu	Leu	Glu	Ala	Thr	Ile	Met
				905					910					915
Ser	Gly	Ser	Thr	Met	Ser	Leu	Asn	His	Glu	Ala	Pro	Thr	Pro	Arg
				920					925					930
Ser	Gln	Leu	Gly	Arg	Gln	Ala	Ser	Phe	Gln	Glu	Arg	Ser	Ser	Ser
				935					940					945
Arg	Pro	His	Tyr	Ser	Gln	Thr	Thr	Arg	Ser	Asn	Thr	Leu	Pro	Ser
				950					955					960
Asp	Val	Gly	Arg	Lys	Ser	Val	Thr	Leu	Arg	Lys	Met	Lys	Gln	Glu
				965					970					975
Ile	Lys	Glu	Ile	Met	Ser	Pro	Thr	Pro	Val	Glu	Leu	His	Lys	Val
				980					985					990
Thr	Leu	Tyr	Lys	Asp	Ser	Asp	Met	Glu	Asp	Phe	Gly	Phe	Ser	Val
				995					1000					1005
Ala	Asp	Gly	Leu	Leu	Glu	Lys	Gly	Val	Tyr	Val	Lys	Asn	Ile	Arg
				1010					1015					1020
Pro	Ala	Gly	Pro	Gly	Asp	Leu	Gly	Gly	Leu	Lys	Pro	Tyr	Asp	Arg
				1025					1030					1035
Leu	Leu	Gln	Val	Asn	His	Val	Arg	Thr	Arg	Asp	Phe	Asp	Cys	Cys
				1040					1045					1050
Leu	Val	Val	Pro	Leu	Ile	Ala	Glu	Ser	Gly	Asn	Lys	Leu	Asp	Leu
				1055					1060					1065
Val	Ile	Ser	Arg	Asn	Pro	Leu	Ala	Ser	Gln	Lys	Ser	Ile	Asp	Gln
				1070					1075					1080
Gln	Ser	Leu	Pro	Gly	Asp	Trp	Ser	Glu	Gln	Asn	Ser	Ala	Phe	Phe
				1085					1090					1095
Gln	Gln	Pro	Ser	His	Gly	Gly	Asn	Leu	Glu	Thr	Arg	Glu	Pro	Thr
				1100					1105					1110
Asn	Thr	Leu												

<210> 37
 <211> 511
 <212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1338201CD1

<400> 37

Met	Ser	Arg	Gly	Pro	Glu	Glu	Val	Asn	Arg	Leu	Thr	Glu	Ser	Thr
1				5					10					15
Tyr	Arg	Asn	Val	Met	Glu	Gln	Phe	Asn	Pro	Gly	Leu	Arg	Asn	Leu
				20					25					30
Ile	Asn	Leu	Gly	Lys	Asn	Tyr	Glu	Lys	Ala	Val	Asn	Ala	Met	Ile
				35					40					45
Leu	Ala	Gly	Lys	Ala	Tyr	Tyr	Asp	Gly	Val	Ala	Lys	Ile	Gly	Glu
				50					55					60
Ile	Ala	Thr	Gly	Ser	Pro	Val	Ser	Thr	Glu	Leu	Gly	His	Val	Leu
				65					70					75
Ile	Glu	Ile	Ser	Ser	Thr	His	Lys	Lys	Leu	Asn	Glu	Ser	Leu	Asp
				80					85					90
Glu	Asn	Phe	Lys	Lys	Phe	His	Lys	Glu	Ile	Ile	His	Glu	Leu	Glu
				95					100					105
Lys	Lys	Ile	Glu	Leu	Asp	Val	Lys	Tyr	Met	Asn	Ala	Thr	Leu	Lys
				110					115					120
Arg	Tyr	Gln	Thr	Glu	His	Lys	Asn	Lys	Leu	Glu	Ser	Leu	Glu	Lys
				125					130					135
Ser	Gln	Ala	Glu	Leu	Lys	Lys	Ile	Arg	Arg	Lys	Ser	Gln	Gly	Ser
				140					145					150
Arg	Asn	Ala	Leu	Lys	Tyr	Glu	His	Lys	Glu	Ile	Glu	Tyr	Val	Glu
				155					160					165
Thr	Val	Thr	Ser	Arg	Gln	Ser	Glu	Ile	Gln	Lys	Phe	Ile	Ala	Asp
				170					175					180
Gly	Cys	Lys	Glu	Ala	Leu	Leu	Glu	Glu	Lys	Arg	Arg	Phe	Cys	Phe
				185					190					195
Leu	Val	Asp	Lys	His	Cys	Gly	Phe	Ala	Asn	His	Ile	His	Tyr	Tyr
				200					205					210
His	Leu	Gln	Ser	Ala	Glu	Leu	Leu	Asn	Ser	Lys	Leu	Pro	Arg	Trp
				215					220					225
Gln	Glu	Thr	Cys	Val	Asp	Ala	Ile	Lys	Val	Pro	Glu	Lys	Ile	Met
				230					235					240
Asn	Met	Ile	Glu	Glu	Ile	Lys	Thr	Pro	Ala	Ser	Thr	Pro	Val	Ser
				245					250					255
Gly	Thr	Pro	Gln	Ala	Ser	Pro	Met	Ile	Glu	Arg	Ser	Asn	Val	Val
				260					265					270
Arg	Lys	Asp	Tyr	Asp	Thr	Leu	Ser	Lys	Cys	Ser	Pro	Lys	Met	Pro
				275					280					285
Pro	Ala	Pro	Ser	Gly	Arg	Ala	Tyr	Thr	Ser	Pro	Leu	Ile	Asp	Met
				290					295					300
Phe	Asn	Asn	Pro	Ala	Thr	Ala	Ala	Pro	Asn	Ser	Gln	Arg	Val	Asn
				305					310					315
Asn	Ser	Thr	Gly	Thr	Ser	Glu	Asp	Pro	Ser	Leu	Gln	Arg	Ser	Val
				320					325					330
Ser	Val	Ala	Thr	Gly	Leu	Asn	Met	Met	Lys	Lys	Gln	Lys	Val	Lys
				335					340					345
Thr	Ile	Phe	Pro	His	Thr	Ala	Gly	Ser	Asn	Lys	Thr	Leu	Leu	Ser
				350					355					360
Phe	Ala	Gln	Gly	Asp	Val	Ile	Thr	Leu	Leu	Ile	Pro	Glu	Glu	Lys
				365					370					375
Asp	Gly	Trp	Leu	Tyr	Gly	Glu	His	Asp	Val	Ser	Lys	Ala	Arg	Gly
				380					385					390
Trp	Phe	Pro	Ser	Ser	Tyr	Thr	Lys	Leu	Leu	Glu	Glu	Asn	Glu	Thr
				395					400					405
Glu	Ala	Val	Thr	Val	Pro	Thr	Pro	Ser	Pro	Thr	Pro	Val	Arg	Ser
				410					415					420
Ile	Ser	Thr	Val	Asn	Leu	Ser	Glu	Asn	Ser	Ser	Val	Val	Ile	Pro
				425					430					435
Pro	Pro	Asp	Tyr	Leu	Glu	Cys	Leu	Ser	Met	Gly	Ala	Ala	Ala	Asp
				440					445					450

Arg	Arg	Ala	Asp	Ser	Ala	Arg	Thr	Thr	Ser	Thr	Phe	Lys	Ala	Pro
				455					460					465
Ala	Ser	Lys	Pro	Glu	Thr	Ala	Ala	Pro	Asn	Asp	Ala	Asn	Gly	Thr
				470					475					480
Ala	Lys	Pro	Pro	Phe	Leu	Ser	Gly	Glu	Asn	Pro	Phe	Ala	Thr	Val
				485					490					495
Lys	Leu	Arg	Pro	Thr	Val	Thr	Asn	Asp	Arg	Ser	Ala	Pro	Ile	Ile
				500					505					510

Arg

<210> 38

<211> 1177

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1405141CD1

<400> 38

Met	Thr	Thr	Ile	Leu	Lys	Pro	Ser	Ala	Asp	Phe	Leu	Thr	Ser	Asn
1				5					10					15
Lys	Leu	Leu	Lys	Tyr	Ser	Trp	Phe	Phe	Phe	Asp	Val	Leu	Ile	Lys
				20					25					30
Ser	Met	Ala	Gln	His	Leu	Ile	Glu	Asn	Ser	Lys	Val	Lys	Leu	Leu
				35					40					45
Arg	Asn	Gln	Arg	Phe	Pro	Ala	Ser	Tyr	His	His	Ala	Val	Glu	Thr
				50					55					60
Val	Val	Asn	Met	Leu	Met	Pro	His	Ile	Thr	Gln	Lys	Phe	Arg	Asp
				65					70					75
Asn	Pro	Glu	Ala	Ser	Lys	Asn	Ala	Asn	His	Ser	Leu	Ala	Val	Phe
				80					85					90
Ile	Lys	Arg	Cys	Phe	Thr	Phe	Met	Asp	Arg	Gly	Phe	Val	Phe	Lys
				95					100					105
Gln	Ile	Asn	Asn	Tyr	Ile	Ser	Cys	Phe	Ala	Pro	Gly	Asp	Pro	Lys
				110					115					120
Thr	Leu	Phe	Glu	Tyr	Lys	Phe	Glu	Phe	Leu	Arg	Val	Val	Cys	Asn
				125					130					135
His	Glu	His	Tyr	Ile	Pro	Leu	Asn	Leu	Pro	Met	Pro	Phe	Gly	Lys
				140					145					150
Gly	Arg	Ile	Gln	Arg	Tyr	Gln	Asp	Leu	Gln	Leu	Asp	Tyr	Ser	Leu
				155					160					165
Thr	Asp	Glu	Phe	Cys	Arg	Asn	His	Phe	Leu	Val	Gly	Leu	Leu	Leu
				170					175					180
Arg	Glu	Val	Gly	Thr	Ala	Leu	Gln	Glu	Phe	Arg	Glu	Val	Arg	Leu
				185					190					195
Ile	Ala	Ile	Ser	Val	Leu	Lys	Asn	Leu	Leu	Ile	Lys	His	Ser	Phe
				200					205					210
Asp	Asp	Arg	Tyr	Ala	Ser	Arg	Ser	His	Gln	Ala	Arg	Ile	Ala	Thr
				215					220					225
Leu	Tyr	Leu	Pro	Leu	Phe	Gly	Leu	Leu	Ile	Glu	Asn	Val	Gln	Arg
				230					235					240
Ile	Asn	Val	Arg	Asp	Val	Ser	Pro	Phe	Pro	Val	Asn	Ala	Gly	Met
				245					250					255
Thr	Val	Lys	Asp	Glu	Ser	Leu	Ala	Leu	Pro	Ala	Val	Asn	Pro	Leu
				260					265					270
Val	Thr	Pro	Gln	Lys	Gly	Ser	Thr	Leu	Asp	Asn	Ser	Leu	His	Lys
				275					280					285
Asp	Leu	Leu	Gly	Ala	Ile	Ser	Gly	Ile	Ala	Ser	Pro	Tyr	Thr	Thr
				290					295					300
Ser	Thr	Pro	Asn	Ile	Asn	Ser	Val	Arg	Asn	Ala	Asp	Ser	Arg	Gly
				305					310					315
Ser	Leu	Ile	Ser	Thr	Asp	Ser	Gly	Asn	Ser	Leu	Pro	Glu	Arg	Asn
				320					325					330
Ser	Glu	Lys	Ser	Asn	Ser	Leu	Asp	Lys	His	Gln	Gln	Ser	Ser	Thr
				335					340					345
Leu	Gly	Asn	Ser	Val	Val	Arg	Cys	Asp	Lys	Leu	Asp	Gln	Ser	Glu

Ile Lys Ser Leu	350	Leu Met Cys Phe Leu	355	Ile Leu Lys Ser	360
Ser Asp Asp Ala	365	Leu Phe Thr Tyr Trp	370	Met	375
Glu Leu Met Asp	380	Asn Lys Ala Ser Thr	385	Ser	390
Phe Gln Tyr Met	395	Glu Val Cys Leu His	400	Gln	405
Ser Ser Val Leu	410	Ala Ser Val Arg Lys	415	Ile	420
Asp Ala Asp Val	425	Asn Gly Tyr Gly His	430	Ser	435
Thr Glu Val Cys	440	Leu Glu Ala Asn Ile	445	Ala	450
Leu Ala Phe Lys	455	Leu Ser Leu Phe	460	Thr	465
Leu Met Lys Lys	470	Asn His Gly His Asn	475	Pro	480
His Gln Ser Glu	485	Val Cys Phe Leu Gln	490	Lys	495
Ser Leu Ile Tyr	500	Thr Ala Leu Lys Asn	505	Val	510
Asp Met Cys Ala	515	Phe Phe Pro Ser Thr	520	Phe	525
Ser Lys Leu Ser	530	Ile Leu Cys Tyr Glu	535	Ile	540
Phe Leu Met Arg	545	Ser Ile Arg Thr Glu	550	Ala	555
Val Arg Thr His	560	Asn Asn Phe Asp Tyr	565	Gly	570
Ala Asp Val Val	575	Leu Gln Val Ile Ile	580	Ser	585
Ser Ile Ile Asn	590	Gly Ile Gly Gly Thr	595	Arg	600
Thr Ser Phe Ser	605	Asn Cys Ala Asn Ser	610	Asp	615
Thr Val Leu Met	620	Ser Asp Val Lys Asp	625	Leu	630
Pro Glu Met Leu	635	Ala Thr Ala Gln Met	640	Lys	645
Ala Ser Thr Pro	650	Val Asp Leu Gln Tyr	655	Ser	660
Arg Ile His Val	665	Glu Leu Arg Lys Thr	670	Trp	675
Tyr Val His Val	680	Lys Asn Gly Asp Leu	685	Ser	690
Gly Val Phe Arg	695	Thr Ala Leu Val Ala	700	Glu	705
Asn Ile Asp Glu	710	Gln Gly Cys Thr Ala	715	Phe	720
Asp Val His Phe	725	Glu Ala Ser Met Met	730	Glu	735
Cys Ala Asp Gly	740	Asn Glu Asp Val Leu	745	Met	750
Asp Ile Tyr Lys	755	Leu Trp Lys Ala Glu	760	Arg	765
Phe Glu Arg Leu	770	Ile Ile Ile Pro Ile	775	Tyr	780
Ser Lys Val Thr	785	Thr Leu His Arg Ala	790	Thr	795
Thr Tyr Phe Arg	800	Gly Arg Ser Val Leu	805	Gly	810
Glu Asp Gly Lys	815	Val Ala Phe Phe Gly	820	Gln	825
Leu Ser Glu Ile	830	Glu Tyr Ile Tyr Lys	835	Glu	840
	845	Ser Gln Arg Leu Leu	850	Lys	855

Phe	Gly	Ser	Glu	Asn	Val	Lys	Met	Ile	Gln	Asp	Ser	Gly	Lys	Val
				860					865					870
Asn	Pro	Lys	Asp	Leu	Asp	Ser	Lys	Tyr	Ala	Tyr	Ile	Gln	Val	Thr
				875					880					885
His	Val	Ile	Pro	Phe	Phe	Asp	Glu	Lys	Glu	Leu	Gln	Glu	Arg	Lys
				890					895					900
Thr	Glu	Phe	Glu	Arg	Ser	His	Asn	Ile	Arg	Arg	Phe	Met	Phe	Glu
				905					910					915
Met	Pro	Phe	Thr	Gln	Thr	Gly	Lys	Arg	Gln	Gly	Gly	Val	Glu	Glu
				920					925					930
Gln	Cys	Lys	Arg	Arg	Thr	Ile	Leu	Thr	Ala	Ile	His	Cys	Phe	Pro
				935					940					945
Tyr	Val	Lys	Lys	Arg	Ile	Pro	Val	Met	Tyr	Gln	His	His	Thr	Asp
				950					955					960
Leu	Asn	Pro	Ile	Glu	Val	Ala	Ile	Asp	Glu	Met	Ser	Lys	Lys	Val
				965					970					975
Ala	Glu	Leu	Arg	Gln	Leu	Cys	Ser	Ser	Ala	Glu	Val	Asp	Met	Ile
				980					985					990
Lys	Leu	Gln	Leu	Lys	Leu	Gln	Gly	Ser	Val	Ser	Val	Gln	Val	Asn
				995					1000					1005
Ala	Gly	Pro	Leu	Ala	Tyr	Ala	Arg	Ala	Phe	Leu	Asp	Asp	Thr	Asn
				1010					1015					1020
Thr	Lys	Arg	Tyr	Pro	Asp	Asn	Lys	Val	Lys	Leu	Leu	Lys	Glu	Val
				1025					1030					1035
Phe	Arg	Gln	Phe	Val	Glu	Ala	Cys	Gly	Gln	Ala	Leu	Ala	Val	Asn
				1040					1045					1050
Glu	Arg	Leu	Ile	Lys	Glu	Asp	Gln	Leu	Glu	Tyr	Gln	Glu	Glu	Met
				1055					1060					1065
Lys	Ala	Asn	Tyr	Arg	Glu	Met	Ala	Lys	Glu	Leu	Ser	Glu	Ile	Met
				1070					1075					1080
His	Glu	Gln	Ile	Cys	Pro	Leu	Glu	Asp	Glu	Asp	Glu	Arg	Leu	Thr
				1085					1090					1095
Glu	Phe	Pro	Ser	His	Leu	Gln	Arg	His	Gln	Trp	Asp	Ser	Asn	Lys
				1100					1105					1110
His	Asn	Gly	Ser	Arg	Asp	Asp	Gln	Leu	Val	Phe	Gly	Arg	Val	Ile
				1115					1120					1125
Thr	Ser	His	Gly	Pro	Cys	Val	Gly	Thr	Cys	Phe	Val	Ile	Cys	Lys
				1130					1135					1140
Leu	Arg	Met	Leu	Ser	Lys	Ala	Asn	His	Trp	Gly	Asp	Arg	Ala	Gln
				1145					1150					1155
Gly	Gly	Pro	Arg	Gly	Arg	Gly	Glu	Lys	Gly	Asn	Lys	Glu	Gln	Arg
				1160					1165					1170
Tyr	Phe	Leu	Thr	Asp	Phe	Leu								
				1175										

<210> 39

<211> 665

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1686305CD1

<400> 39

Met	Thr	Ser	Ala	Asn	Lys	Ala	Ile	Glu	Leu	Gln	Leu	Gln	Val	Lys
1				5					10					15
Gln	Asn	Ala	Glu	Glu	Leu	Gln	Asp	Phe	Met	Arg	Asp	Leu	Glu	Asn
				20					25					30
Trp	Glu	Lys	Asp	Ile	Lys	Gln	Lys	Asp	Met	Glu	Leu	Arg	Arg	Gln
				35					40					45
Asn	Gly	Val	Pro	Glu	Glu	Asn	Leu	Pro	Pro	Ile	Arg	Asn	Gly	Asn
				50					55					60
Phe	Arg	Lys	Lys	Lys	Lys	Gly	Lys	Ala	Lys	Glu	Ser	Ser	Lys	Lys
				65					70					75
Thr	Arg	Glu	Glu	Asn	Thr	Lys	Asn	Arg	Ile	Lys	Ser	Tyr	Asp	Tyr
				80					85					90
Glu	Ala	Trp	Ala	Lys	Leu	Asp	Val	Asp	Arg	Ile	Leu	Asp	Glu	Leu

Asp Lys Asp Asp	95	Thr His Glu Ser	100	Leu Ser Gln Glu Ser	105
Ser Glu Glu Asp	110	Ile His Val Asp	115	Ser Gln Lys Ala Leu	120
Leu Lys Glu Lys	125	Asn Lys Tyr Phe	130	Lys Gln Gly Lys Tyr	135
Glu Ala Ile Asp	140	Cys Tyr Thr Lys Gly	145	Met Asp Ala Asp Pro	150
Asn Pro Val Leu	155	Pro Thr Asn Arg Ala	160	Ser Ala Tyr Phe Arg	165
Lys Lys Phe Ala	170	Val Ala Glu Ser Asp	175	Cys Asn Leu Ala Val	180
Leu Asn Arg Ser	185	Tyr Thr Lys Ala Tyr	190	Ser Arg Arg Gly Ala	195
Arg Phe Ala Leu	200	Gln Lys Leu Glu Glu	205	Ala Lys Lys Asp Tyr	210
Arg Val Leu Glu	215	Leu Glu Pro Asn Asn	220	Phe Glu Ala Thr Asn	225
Leu Arg Lys Ile	230	Ser Gln Ala Leu Ala	235	Ser Lys Glu Asn Ser	240
Pro Lys Glu Ala	245	Asp Ile Val Ile Lys	250	Ser Thr Glu Gly Glu	255
Lys Gln Ile Glu	260	Ala Gln Gln Asn Lys	265	Gln Gln Ala Ile Ser	270
Lys Asp Arg Gly	275	Asn Gly Phe Phe Lys	280	Glu Gly Lys Tyr Glu	285
Ala Ile Glu Cys	290	Tyr Thr Arg Gly Ile	295	Ala Ala Asp Gly Ala	300
Ala Leu Leu Pro	305	Ala Asn Arg Ala Met	310	Tyr Leu Lys Ile Gln	315
Lys Tyr Glu Glu	320	Ala Glu Lys Asp Cys	325	Thr Gln Ala Ile Leu	330
Asp Gly Ser Tyr	335	Ser Lys Ala Phe Ala	340	Arg Arg Gly Thr Ala	345
Thr Phe Leu Gly	350	Lys Leu Asn Glu Ala	355	Lys Gln Asp Phe Glu	360
Val Leu Leu Leu	365	Glu Pro Gly Asn Lys	370	Gln Ala Val Thr Glu	375
Ser Lys Ile Lys	380	Lys Glu Leu Ile Glu	385	Gly His Trp Asp Asp	390
Val Phe Leu Asp	395	Ser Thr Gln Arg Gln	400	Asn Val Val Lys Pro	405
Asp Asn Pro Pro	410	His Pro Gly Ser Thr	415	Lys Pro Leu Lys Lys	420
Ile Ile Glu Glu	425	Thr Gly Asn Leu Ile	430	Gln Thr Ile Asp Val	435
Asp Ser Thr Thr	440	Ala Ala Ala Pro Glu	445	Asn Asn Pro Ile Asn	450
Ala Asn Val Ile	455	Ala Ala Thr Gly Thr	460	Thr Ser Lys Lys Asn	465
Ser Gln Asp Asp	470	Leu Phe Pro Thr Ser	475	Asp Thr Pro Arg Ala	480
Val Leu Lys Ile	485	Glu Glu Val Ser Asp	490	Thr Ser Ser Leu Gln	495
Gln Ala Ser Leu	500	Lys Gln Asp Val Cys	505	Gln Ser Tyr Ser Glu	510
Met Pro Ile Glu	515	Ile Glu Gln Lys Pro	520	Ala Gln Phe Ala Thr	525
Val Leu Pro Pro	530	Ile Pro Ala Asn Ser	535	Phe Gln Leu Glu Ser	540
Phe Arg Gln Leu	545	Lys Ser Ser Pro Asp	550	Met Leu Tyr Gln Tyr	555
Lys Gln Ile Glu	560	Pro Ser Leu Tyr Pro	565	Lys Leu Phe Gln Lys	570
Leu Asp Pro Asp	575	Val Phe Asn Gln Ile	580	Val Lys Ile Leu His	585
	590		595		600

Phe	Tyr	Ile	Glu	Lys	Glu	Lys	Pro	Leu	Leu	Ile	Phe	Glu	Ile	Leu
				605					610					615
Gln	Arg	Leu	Ser	Glu	Leu	Lys	Arg	Phe	Asp	Met	Ala	Val	Met	Phe
				620					625					630
Met	Ser	Glu	Thr	Glu	Lys	Lys	Ile	Ala	Arg	Ala	Leu	Phe	Asn	His
				635					640					645
Ile	Asp	Lys	Ser	Gly	Leu	Lys	Asp	Ser	Ser	Val	Glu	Glu	Leu	Lys
				650					655					660
Lys	Arg	Tyr	Gly	Gly										
				665										

<210> 40

<211> 125

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1688972CD1

<400> 40

Met	Leu	Asp	Leu	Gln	Lys	Gln	Leu	Gly	Arg	Phe	Pro	Gly	Thr	Phe
1				5					10					15
Val	Gly	Thr	Thr	Glu	Pro	Ala	Ser	Pro	Pro	Leu	Ser	Ser	Thr	Ser
				20					25					30
Pro	Thr	Thr	Ala	Ala	Ala	Thr	Met	Pro	Val	Val	Pro	Ser	Val	Ala
				35					40					45
Ser	Leu	Ala	Pro	Pro	Gly	Glu	Ala	Ser	Leu	Cys	Leu	Glu	Glu	Val
				50					55					60
Ala	Pro	Pro	Ala	Ser	Gly	Thr	Arg	Lys	Ala	Arg	Val	Leu	Tyr	Asp
				65					70					75
Tyr	Glu	Ala	Ala	Asp	Ser	Ser	Glu	Leu	Ala	Leu	Leu	Ala	Asp	Glu
				80					85					90
Leu	Ile	Thr	Val	Tyr	Ser	Leu	Pro	Gly	Met	Asp	Pro	Asp	Trp	Leu
				95					100					105
Ile	Gly	Glu	Arg	Gly	Asn	Lys	Lys	Gly	Lys	Val	Pro	Val	Thr	Tyr
				110					115					120
Leu	Glu	Leu	Leu	Ser										
				125										

<210> 41

<211> 366

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1812494CD1

<400> 41

Met	Cys	Tyr	Phe	Tyr	Leu	Gly	Asp	Lys	Ile	Lys	Thr	Ile	Ser	Phe
1				5					10					15
Gln	Ala	Phe	Ile	Leu	Met	His	Leu	Leu	Leu	Pro	Ser	Glu	Tyr	Ser
				20					25					30
Leu	Asp	Gly	Phe	His	Met	Ser	Gly	Phe	Ser	Leu	Gly	Ser	Gly	Ser
				35					40					45
Glu	Gly	Glu	Asp	Gly	Phe	Gln	Val	Glu	Leu	Glu	Leu	Val	Glu	Leu
				50					55					60
Thr	Val	Gly	Thr	Leu	Asp	Leu	Cys	Glu	Ser	Glu	Val	Leu	Pro	Lys
				65					70					75
Arg	Arg	Arg	Arg	Lys	Arg	Asn	Lys	Lys	Glu	Lys	Ser	Arg	Asp	Gln
				80					85					90
Glu	Ala	Gly	Ala	His	Arg	Thr	Leu	Leu	Gln	Gln	Thr	Gln	Glu	Glu
				95					100					105
Glu	Pro	Ser	Thr	Gln	Ser	Ser	Gln	Ala	Val	Ala	Ala	Pro	Leu	Gly
				110					115					120
Pro	Leu	Leu	Asp	Glu	Ala	Lys	Ala	Pro	Gly	Gln	Pro	Glu	Leu	Trp
				125					130					135
Asn	Ala	Leu	Leu	Ala	Ala	Cys	Arg	Ala	Gly	Asp	Val	Gly	Val	Leu

Lys	Leu	Gln	Leu	140	Ala	Pro	Ser	Pro	Ala	145	Asp	Pro	Arg	Val	Leu	150	Ser
				155						160							165
Leu	Leu	Ser	Ala	170	Pro	Leu	Gly	Ser	Gly	175	Phe	Thr	Leu	Leu			His
Ala	Ala	Ala	Ala	185	Ala	Gly	Arg	Gly	Ser	190	Val	Val	Arg	Leu	Leu		Leu
Glu	Ala	Gly	Ala	200	Asp	Pro	Thr	Val	Gln	205	Asp	Ser	Arg	Ala	Arg		Pro
Pro	Tyr	Thr	Val	215	Ala	Ala	Asp	Lys	Ser	220	Thr	Arg	Asn	Glu	Phe		Arg
Arg	Phe	Met	Glu	230	Lys	Asn	Pro	Asp	Ala	235	Tyr	Asp	Tyr	Asn	Lys		Ala
Gln	Val	Pro	Gly	245	Pro	Leu	Thr	Pro	Glu	250	Met	Glu	Ala	Arg	Gln		Ala
Thr	Arg	Lys	Arg	260	Glu	Gln	Lys	Ala	Ala	265	Arg	Arg	Gln	Arg	Glu		Glu
Gln	Gln	Gln	Arg	275	Gln	Gln	Glu	Gln	Glu	280	Glu	Arg	Glu	Arg	Glu		Glu
Gln	Arg	Arg	Phe	290	Ala	Ala	Leu	Ser	Asp	295	Arg	Glu	Lys	Arg	Ala		Leu
Ala	Ala	Glu	Arg	305	Arg	Leu	Ala	Ala	Gln	310	Leu	Gly	Ala	Pro	Thr		Ser
Pro	Ile	Pro	Asp	320	Ser	Ala	Ile	Val	Asn	325	Thr	Arg	Arg	Cys	Trp		Ser
Cys	Gly	Ala	Ser	335	Leu	Gln	Gly	Leu	Thr	340	Pro	Phe	His	Tyr	Leu		Asp
Phe	Ser	Phe	Cys	350	Ser	Thr	Arg	Cys	Leu	355	Gln	Asp	His	Arg	Arg		Gln
Ala	Gly	Arg	Pro	365	Ser	Ser											

<210> 42

<211> 173

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2013853CD1

<400> 42

Met	Ser	Thr	Met	Gly	Asn	Glu	Ala	Ser	Tyr	Pro	Ala	Glu	Met	Cys
1				5					10					15
Ser	His	Phe	Asp	Asn	Asp	Glu	Ile	Lys	Arg	Leu	Gly	Arg	Arg	Phe
				20					25					30
Lys	Lys	Leu	Asp	Leu	Asp	Lys	Ser	Gly	Ser	Leu	Ser	Val	Glu	Glu
				35					40					45
Phe	Met	Ser	Leu	Pro	Glu	Leu	Arg	His	Asn	Pro	Leu	Val	Arg	Arg
				50					55					60
Val	Ile	Asp	Val	Phe	Asp	Thr	Asp	Gly	Asp	Gly	Glu	Val	Asp	Phe
				65					70					75
Lys	Glu	Phe	Ile	Leu	Gly	Thr	Ser	Gln	Phe	Ser	Val	Lys	Gly	Asp
				80					85					90
Glu	Glu	Gln	Lys	Leu	Arg	Phe	Ala	Phe	Ser	Ile	Tyr	Asp	Met	Asp
				95					100					105
Lys	Asp	Gly	Tyr	Ile	Ser	Asn	Gly	Glu	Leu	Phe	Gln	Val	Leu	Lys
				110					115					120
Met	Met	Val	Gly	Asn	Asn	Leu	Thr	Asp	Trp	Gln	Leu	Gln	Gln	Leu
				125					130					135
Val	Asp	Lys	Thr	Ile	Ile	Ile	Leu	Asp	Lys	Asp	Gly	Asp	Gly	Lys
				140					145					150
Ile	Ser	Phe	Glu	Glu	Phe	Ser	Ala	Val	Val	Arg	Asp	Leu	Glu	Ile
				155					160					165
His	Lys	Lys	Leu	Val	Leu	Ile	Val							
				170										

<210> 43

<211> 761

<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2284925CD1

<400> 43

Met	Arg	Leu	Thr	Gln	Asp	Pro	Ile	Gln	Val	Leu	Leu	Ile	Phe	Ala	1	5	10	15
Lys	Glu	Asp	Ser	Gln	Ser	Asp	Gly	Phe	Trp	Trp	Ala	Cys	Asp	Arg	20	25	30	35
Ala	Gly	Tyr	Arg	Cys	Asn	Ile	Ala	Arg	Thr	Pro	Glu	Ser	Ala	Leu	40	45	50	55
Glu	Cys	Phe	Leu	Asp	Lys	His	His	Glu	Ile	Ile	Val	Ile	Asp	His	60	65	70	75
Arg	Gln	Thr	Gln	Asn	Phe	Asp	Ala	Glu	Ala	Val	Cys	Arg	Ser	Ile	80	85	90	95
Arg	Ala	Thr	Asn	Pro	Ser	Glu	His	Thr	Val	Ile	Leu	Ala	Val	Val	100	105	110	115
Ser	Arg	Val	Ser	Asp	Asp	His	Glu	Glu	Ala	Ser	Val	Leu	Pro	Leu	120	125	130	135
Leu	His	Ala	Gly	Phe	Asn	Arg	Arg	Phe	Met	Glu	Asn	Ser	Ser	Ile	140	145	150	155
Ile	Ala	Cys	Tyr	Asn	Glu	Leu	Ile	Gln	Ile	Glu	His	Gly	Glu	Val	160	165	170	175
Arg	Ser	Gln	Phe	Lys	Leu	Arg	Ala	Cys	Asn	Ser	Val	Phe	Thr	Ala	180	185	190	195
Leu	Asp	His	Cys	His	Glu	Ala	Ile	Glu	Ile	Thr	Ser	Asp	Asp	His	200	205	210	215
Val	Ile	Gln	Tyr	Val	Asn	Pro	Ala	Phe	Glu	Arg	Met	Met	Gly	Tyr	220	225	230	235
His	Lys	Gly	Glu	Leu	Leu	Gly	Lys	Glu	Leu	Ala	Asp	Leu	Pro	Lys	240	245	250	255
Ser	Asp	Lys	Asn	Arg	Ala	Asp	Leu	Leu	Asp	Thr	Ile	Asn	Thr	Cys	260	265	270	275
Ile	Lys	Lys	Gly	Lys	Glu	Trp	Gln	Gly	Val	Tyr	Tyr	Ala	Arg	Arg	280	285	290	295
Lys	Ser	Gly	Asp	Ser	Ile	Gln	Gln	His	Val	Lys	Ile	Thr	Pro	Val	300	305	310	315
Ile	Gly	Gln	Gly	Gly	Lys	Ile	Arg	His	Phe	Val	Ser	Leu	Lys	Lys	320	325	330	335
Leu	Cys	Cys	Thr	Thr	Asp	Asn	Asn	Lys	Gln	Ile	His	Lys	Ile	His	340	345	350	355
Arg	Asp	Ser	Gly	Asp	Asn	Ser	Gln	Thr	Glu	Pro	His	Ser	Phe	Arg	360	365	370	375
Tyr	Lys	Asn	Arg	Arg	Lys	Glu	Ser	Ile	Asp	Val	Lys	Ser	Ile	Ser	380	385	390	395
Ser	Arg	Gly	Ser	Asp	Ala	Pro	Ser	Leu	Gln	Asn	Arg	Arg	Tyr	Pro	400	405	410	415
Ser	Met	Ala	Arg	Ile	His	Ser	Met	Thr	Ile	Glu	Ala	Pro	Ile	Thr	420	425	430	435
Lys	Val	Ile	Asn	Ile	Ile	Asn	Ala	Ala	Gln	Glu	Asn	Ser	Pro	Val	440	445	450	455
Thr	Val	Ala	Glu	Ala	Leu	Asp	Arg	Val	Leu	Glu	Ile	Leu	Arg	Thr	460	465	470	475
Thr	Glu	Leu	Tyr	Ser	Pro	Gln	Leu	Gly	Thr	Lys	Asp	Glu	Asp	Pro	480	485	490	495
His	Thr	Ser	Asp	Leu	Val	Gly	Gly	Leu	Met	Thr	Asp	Gly	Leu	Arg	500	505	510	515
Arg	Leu	Ser	Gly	Asn	Glu	Tyr	Val	Phe	Thr	Lys	Asn	Val	His	Gln	520	525	530	535
Ser	His	Ser	His	Leu	Ala	Met	Pro	Ile	Thr	Ile	Asn	Asp	Val	Pro	540	545	550	555
Pro	Cys	Ile	Ser	Gln	Leu	Leu	Asp	Asn	Glu	Glu	Ser	Trp	Asp	Phe	560	565	570	575
Asn	Ile	Phe	Glu	Leu	Glu	Ala	Ile	Thr	His	Lys	Arg	Pro	Leu	Val	580	585	590	595

	440		445		450
Tyr Leu Gly Leu	Lys Val Phe Ser Arg	Phe Gly Val Cys Glu	Phe		
	455		460		465
Leu Asn Cys Ser	Glu Thr Thr Leu Arg	Ala Trp Phe Gln Val	Ile		
	470		475		480
Glu Ala Asn Tyr	His Ser Ser Asn Ala	Tyr His Asn Ser Thr	His		
	485		490		495
Ala Ala Asp Val	Leu His Ala Thr Ala	Phe Phe Leu Gly Lys	Glu		
	500		505		510
Arg Val Lys Gly	Ser Leu Asp Gln Leu	Asp Glu Val Ala Ala	Leu		
	515		520		525
Ile Ala Ala Thr	Val His Asp Val Asp	His Pro Gly Arg Thr	Asn		
	530		535		540
Ser Phe Leu Cys	Asn Ala Gly Ser Glu	Leu Ala Val Leu Tyr	Asn		
	545		550		555
Asp Thr Ala Val	Leu Glu Ser His His	Thr Ala Leu Ala Phe	Gln		
	560		565		570
Leu Thr Val Lys	Asp Thr Lys Cys Asn	Ile Phe Lys Asn Ile	Asp		
	575		580		585
Arg Asn His Tyr	Arg Thr Leu Arg Gln	Ala Ile Ile Asp Met	Val		
	590		595		600
Leu Ala Thr Glu	Met Thr Lys His Phe	Glu His Val Asn Lys	Phe		
	605		610		615
Val Asn Ser Ile	Asn Lys Pro Met Ala	Ala Glu Ile Glu Gly	Ser		
	620		625		630
Asp Cys Glu Cys	Asn Pro Ala Gly Lys	Asn Phe Pro Glu Asn	Gln		
	635		640		645
Ile Leu Ile Lys	Arg Met Met Ile Lys	Cys Ala Asp Val Ala	Asn		
	650		655		660
Pro Cys Arg Pro	Leu Asp Leu Cys Ile	Glu Trp Ala Gly Arg	Ile		
	665		670		675
Ser Glu Glu Tyr	Phe Ala Gln Thr Asp	Glu Glu Lys Arg Gln	Gly		
	680		685		690
Leu Pro Val Val	Met Pro Val Phe Asp	Arg Asn Thr Cys Ser	Ile		
	695		700		705
Pro Lys Ser Gln	Ile Ser Phe Ile Asp	Phe Ile Thr Asp	Met		
	710		715		720
Phe Asp Ala Trp	Asp Ala Phe Ala His	Leu Pro Ala Leu Met	Gln		
	725		730		735
His Leu Ala Asp	Asn Tyr Lys His Trp	Lys Thr Leu Asp Asp	Leu		
	740		745		750
Lys Cys Lys Ser	Leu Arg Leu Pro Ser	Asp Ser			
	755		760		

<210> 44

<211> 249

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2376728CD1

<400> 44

Met Val Asp Arg	Leu Ala Asn Ser Glu	Ala Asn Thr Arg Arg	Ile
1	5	10	15
Ser Ile Val Glu	Asn Cys Phe Gly Ala	Ala Gly Gln Pro Leu	Thr
	20	25	30
Ile Pro Gly Arg	Val Leu Ile Gly Glu	Gly Val Leu Thr Lys	Leu
	35	40	45
Cys Arg Lys Lys	Pro Lys Ala Arg Gln	Phe Phe Leu Phe Asn	Asp
	50	55	60
Ile Leu Val Tyr	Gly Asn Ile Val Ile	Gln Lys Lys Lys Tyr	Asn
	65	70	75
Lys Gln His Ile	Ile Pro Leu Glu Asn	Val Thr Ile Asp Ser	Ile
	80	85	90
Lys Asp Glu Gly	Asp Leu Arg Asn Gly	Trp Leu Ile Lys Thr	Pro
	95	100	105

Thr	Lys	Ser	Phe	Ala	Val	Tyr	Ala	Ala	Thr	Ala	Thr	Glu	Lys	Ser
				110						115				120
Glu	Trp	Met	Asn	His	Ile	Asn	Lys	Cys	Val	Thr	Asp	Leu	Leu	Ser
				125						130				135
Lys	Ser	Gly	Lys	Thr	Pro	Ser	Asn	Glu	His	Ala	Ala	Val	Trp	Val
				140						145				150
Pro	Asp	Ser	Glu	Ala	Thr	Val	Cys	Met	Arg	Cys	Gln	Lys	Ala	Lys
				155						160				165
Phe	Thr	Pro	Val	Asn	Arg	Arg	His	His	Cys	Arg	Lys	Cys	Gly	Phe
				170						175				180
Val	Val	Cys	Gly	Pro	Cys	Ser	Glu	Lys	Arg	Phe	Leu	Leu	Pro	Ser
				185						190				195
Gln	Ser	Ser	Lys	Pro	Val	Arg	Ile	Cys	Asp	Phe	Cys	Tyr	Asp	Leu
				200						205				210
Leu	Ser	Ala	Gly	Asp	Met	Ala	Thr	Cys	Gln	Pro	Ala	Arg	Ser	Asp
				215						220				225
Ser	Tyr	Ser	Gln	Ser	Leu	Lys	Ser	Pro	Leu	Asn	Asp	Met	Ser	Asp
				230						235				240
Asp	Asp	Asp	Asp	Asp	Asp	Ser	Ser	Asp						
				245										

<210> 45

<211> 247

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2790762CD1

<400> 45

Met	Glu	Thr	Asp	Glu	Ser	Pro	Ser	Pro	Leu	Pro	Cys	Gly	Pro	Ala
1				5					10					15
Gly	Glu	Ala	Val	Met	Glu	Ser	Arg	Ala	Arg	Pro	Phe	Gln	Ala	Leu
				20					25					30
Pro	Arg	Glu	Gln	Ser	Pro	Pro	Pro	Pro	Leu	Gln	Thr	Ser	Ser	Gly
				35					40					45
Ala	Glu	Val	Met	Asp	Val	Gly	Ser	Gly	Asp	Gly	Gln	Ser	Glu	
				50					55					60
Leu	Pro	Ala	Glu	Asp	Pro	Phe	Asn	Phe	Tyr	Gly	Ala	Ser	Leu	Leu
				65					70					75
Ser	Lys	Gly	Ser	Phe	Ser	Lys	Gly	Arg	Leu	Leu	Ile	Asp	Pro	Asn
				80					85					90
Cys	Ser	Gly	His	Ser	Pro	Arg	Thr	Ala	Arg	His	Ala	Pro	Ala	Val
				95					100					105
Arg	Lys	Phe	Ser	Pro	Asp	Leu	Lys	Leu	Leu	Lys	Asp	Val	Lys	Ile
				110					115					120
Ser	Val	Ser	Phe	Thr	Glu	Ser	Cys	Arg	Ser	Lys	Asp	Arg	Lys	Val
				125					130					135
Leu	Tyr	Thr	Gly	Ala	Glu	Arg	Asp	Val	Arg	Ala	Glu	Cys	Gly	Leu
				140					145					150
Leu	Leu	Ser	Pro	Val	Ser	Gly	Asp	Val	His	Ala	Cys	Pro	Phe	Gly
				155					160					165
Gly	Ser	Val	Gly	Asp	Gly	Val	Gly	Ile	Gly	Gly	Glu	Ser	Ala	Asp
				170					175					180
Lys	Lys	Asp	Glu	Glu	Asn	Glu	Leu	Asp	Gln	Glu	Lys	Arg	Val	Glu
				185					190					195
Tyr	Ala	Val	Leu	Asp	Glu	Leu	Glu	Asp	Phe	Thr	Asp	Asn	Leu	Glu
				200					205					210
Leu	Asp	Glu	Glu	Gly	Ala	Gly	Gly	Phe	Thr	Ala	Lys	Ala	Ile	Val
				215					220					225
Gln	Arg	Asp	Arg	Val	Asp	Glu	Glu	Ala	Leu	Asn	Phe	Pro	Tyr	Glu
				230					235					240
Val	Cys	Trp	Gln	Pro	Leu	Leu								
				245										

<210> 46

<211> 316

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2869164CD1

<400> 46

Met	Ala	Glu	Ala	Ala	Leu	Glu	Ala	Val	Arg	Ser	Glu	Leu	Arg	Glu	
1				5					10					15	
Phe	Pro	Ala	Ala	Ala	Arg	Glu	Leu	Cys	Val	Pro	Leu	Ala	Val	Pro	
				20					25					30	
Tyr	Leu	Asp	Lys	Pro	Pro	Thr	Pro	Leu	His	Phe	Tyr	Arg	Asp	Trp	
				35					40					45	
Val	Cys	Pro	Asn	Arg	Pro	Cys	Ile	Ile	Arg	Asn	Ala	Leu	Gln	His	
				50					55					60	
Trp	Pro	Ala	Leu	Gln	Lys	Trp	Ser	Leu	Pro	Tyr	Phe	Arg	Ala	Thr	
				65					70					75	
Val	Gly	Ser	Thr	Glu	Val	Ser	Val	Ala	Val	Thr	Pro	Asp	Gly	Tyr	
				80					85					90	
Ala	Asp	Ala	Val	Arg	Gly	Asp	Arg	Phe	Met	Met	Pro	Ala	Glu	Arg	
				95					100					105	
Arg	Leu	Pro	Leu	Ser	Phe	Val	Leu	Asp	Val	Leu	Glu	Gly	Arg	Ala	
				110					115					120	
Gln	His	Pro	Gly	Val	Leu	Tyr	Val	Gln	Lys	Gln	Cys	Ser	Asn	Leu	
				125					130					135	
Pro	Ser	Glu	Leu	Pro	Gln	Leu	Leu	Pro	Asp	Leu	Glu	Ser	His	Val	
				140					145					150	
Pro	Trp	Ala	Ser	Glu	Ala	Leu	Gly	Lys	Met	Pro	Asp	Ala	Val	Asn	
				155					160					165	
Phe	Trp	Leu	Gly	Glu	Ala	Ala	Ala	Val	Thr	Ser	Leu	His	Lys	Asp	
				170					175					180	
His	Tyr	Glu	Asn	Leu	Tyr	Cys	Val	Val	Ser	Gly	Glu	Lys	His	Phe	
				185					190					195	
Leu	Phe	His	Pro	Pro	Ser	Asp	Arg	Pro	Phe	Ile	Pro	Tyr	Glu	Leu	
				200					205					210	
Tyr	Thr	Pro	Ala	Thr	Tyr	Gln	Leu	Thr	Glu	Glu	Gly	Thr	Phe	Lys	
				215					220					225	
Val	Val	Asp	Glu	Glu	Ala	Met	Glu	Lys	Val	Pro	Trp	Ile	Pro	Leu	
				230					235					240	
Asp	Pro	Leu	Ala	Pro	Asp	Leu	Ala	Arg	Tyr	Pro	Ser	Tyr	Ser	Gln	
				245					250					255	
Ala	Gln	Ala	Leu	Arg	Cys	Thr	Val	Arg	Ala	Gly	Glu	Met	Leu	Tyr	
				260					265					270	
Leu	Pro	Ala	Leu	Trp	Phe	His	His	Val	Gln	Gln	Ser	Gln	Gly	Cys	
				275					280					285	
Ile	Ala	Val	Asn	Phe	Trp	Tyr	Asp	Met	Glu	Tyr	Asp	Leu	Lys	Tyr	
				290					295					300	
Ser	Tyr	Phe	Gln	Leu	Leu	Asp	Ser	Leu	Thr	Lys	Ala	Ser	Gly	Leu	
				305					310					315	

Asp

<210> 47

<211> 334

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3317629CD1

<400> 47

Met	Thr	Arg	Ser	Leu	Phe	Lys	Gly	Asn	Phe	Trp	Ser	Ala	Asp	Ile	
1				5					10					15	
Leu	Ser	Thr	Ile	Gly	Tyr	Asp	Asn	Ile	Ile	Gln	His	Leu	Asn	Asn	
				20					25					30	
Gly	Arg	Lys	Asn	Cys	Lys	Glu	Phe	Glu	Asp	Phe	Leu	Lys	Glu	Arg	
				35					40					45	

Ala Ala Ile Glu Glu Arg Tyr Gly Lys Asp Leu Leu Asn Leu Ser
 50 55 60
 Arg Lys Lys Pro Cys Gly Gln Ser Glu Ile Asn Thr Leu Lys Arg
 65 70 75
 Ala Leu Glu Val Phe Lys Gln Gln Val Asp Asn Val Ala Gln Cys
 80 85 90
 His Ile Gln Leu Ala Gln Ser Leu Arg Glu Ala Arg Lys Met
 95 100 105
 Glu Glu Phe Arg Glu Lys Gln Lys Leu Gln Arg Lys Lys Thr Glu
 110 115 120
 Leu Ile Met Asp Ala Ile His Lys Gln Lys Ser Leu Gln Phe Lys
 125 130 135
 Lys Thr Met Asp Ala Lys Lys Asn Tyr Glu Gln Lys Cys Arg Asp
 140 145 150
 Lys Asp Glu Ala Glu Gln Ala Val Ser Arg Ser Ala Asn Leu Val
 155 160 165
 Asn Pro Lys Gln Gln Glu Lys Leu Phe Val Lys Leu Ala Thr Ser
 170 175 180
 Lys Thr Ala Val Glu Asp Ser Asp Lys Ala Tyr Met Leu His Ile
 185 190 195
 Gly Thr Leu Asp Lys Val Arg Glu Glu Trp Gln Ser Glu His Ile
 200 205 210
 Lys Ala Cys Glu Ala Phe Glu Ala Gln Glu Cys Glu Arg Ile Asn
 215 220 225
 Phe Phe Arg Asn Ala Leu Trp Leu His Val Asn Gln Leu Ser Gln
 230 235 240
 Gln Cys Val Thr Ser Asp Glu Met Tyr Glu Gln Val Arg Lys Ser
 245 250 255
 Leu Glu Met Cys Ser Ile Gln Arg Asp Ile Glu Tyr Phe Val Asn
 260 265 270
 Gln Arg Lys Thr Gly Gln Ile Pro Pro Ala Pro Ile Met Tyr Glu
 275 280 285
 Asn Phe Tyr Ser Ser Gln Lys Asn Ala Val Pro Ala Gly Lys Ala
 290 295 300
 Thr Gly Pro Asn Leu Ala Arg Arg Gly Pro Leu Pro Ile Pro Lys
 305 310 315
 Ser Ser Pro Asp Asp Pro Asn Tyr Ser Leu Val Asp Asp Tyr Ser
 320 325 330
 Leu Leu Tyr Gln

<210> 48

<211> 113

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3870488CD1

<400> 48

Met Asp Pro Lys Leu Leu Lys Gln Leu Arg Lys Ala Glu Lys Ala
 1 5 10 15
 Glu Arg Glu Phe Arg Lys Lys Phe Lys Phe Glu Gly Glu Ile Val
 20 25 30
 Val His Thr Lys Met Met Ile Asp Pro Asn Ala Lys Thr Arg Arg
 35 40 45
 Gly Gly Gly Lys His Leu Gly Ile Arg Arg Gly Glu Ile Leu Glu
 50 55 60
 Val Ile Glu Phe Thr Ser Asn Glu Glu Met Leu Cys Arg Asp Pro
 65 70 75
 Lys Gly Lys Tyr Gly Tyr Val Pro Arg Thr Ala Leu Leu Pro Leu
 80 85 90
 Glu Thr Glu Val Tyr Asp Asp Val Asp Phe Cys Asp Pro Leu Glu
 95 100 105
 Asn Gln Pro Leu Pro Leu Gly Arg

<210> 49

<211> 264
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 3886318CD1

<400> 49
 Met Leu Gly Ala Glu Thr Glu Glu Lys Leu Phe Asp Ala Pro Leu
 1 5 10 15
 Ser Ile Ser Lys Arg Glu Gln Leu Glu Gln Val Pro Glu Asn
 20 25 30
 Tyr Phe Tyr Val Pro Asp Leu Gly Gln Val Pro Glu Ile Asp Val
 35 40 45
 Pro Ser Tyr Leu Pro Asp Leu Pro Gly Ile Ala Asn Asp Leu Met
 50 55 60
 Tyr Ile Ala Asp Leu Gly Pro Gly Ile Ala Pro Ser Ala Pro Gly
 65 70 75
 Thr Ile Pro Glu Leu Pro Thr Phe His Thr Glu Val Ala Glu Pro
 80 85 90
 Leu Lys Ala Asp Leu Gln Asp Gly Val Leu Thr Pro Pro Pro Pro
 95 100 105
 Pro Pro Pro Pro Pro Pro Ala Pro Glu Val Leu Ala Ser Ala Pro
 110 115 120
 Pro Leu Pro Pro Ser Thr Ala Ala Pro Val Gly Gln Gly Ala Arg
 125 130 135
 Gln Asp Asp Ser Ser Ser Ser Ala Ser Pro Ser Val Gln Gly Ala
 140 145 150
 Pro Arg Glu Val Val Asp Pro Ser Gly Gly Arg Ala Thr Leu Leu
 155 160 165
 Glu Ser Ile Arg Gln Ala Gly Gly Ile Gly Lys Ala Lys Leu Arg
 170 175 180
 Ser Met Lys Glu Arg Lys Leu Glu Lys Lys Gln Gln Lys Glu Gln
 185 190 195
 Glu Gln Val Arg Ala Thr Ser Gln Gly Gly His Leu Met Ser Asp
 200 205 210
 Leu Phe Asn Lys Leu Val Met Arg Arg Lys Gly Ile Ser Gly Lys
 215 220 225
 Gly Pro Gly Ala Gly Glu Gly Pro Gly Gly Ala Phe Ala Arg Val
 230 235 240
 Ser Asp Ser Ile Pro Pro Leu Pro Pro Pro Gln Gln Pro Gln Ala
 245 250 255
 Glu Glu Asp Glu Asp Asp Trp Glu Ser
 260

<210> 50
 <211> 185
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 4043934CD1

<400> 50
 Met Gly Gln Cys Leu Arg Tyr Gln Met His Trp Glu Asp Leu Glu
 1 5 10 15
 Glu Tyr Gln Ala Leu Thr Phe Leu Thr Arg Asn Glu Ile Leu Cys
 20 25 30
 Ile His Asp Thr Phe Leu Lys Leu Cys Pro Pro Gly Lys Tyr Tyr
 35 40 45
 Lys Glu Ala Thr Leu Thr Met Asp Gln Val Ser Ser Leu Pro Ala
 50 55 60
 Leu Arg Val Asn Pro Phe Arg Asp Arg Ile Cys Arg Val Phe Ser
 65 70 75
 His Lys Gly Met Phe Ser Phe Glu Asp Val Leu Gly Met Ala Ser
 80 85 90

Val	Phe	Ser	Glu	Gln	Ala	Cys	Pro	Ser	Leu	Lys	Ile	Glu	Tyr	Ala	
				95					100					105	
Phe	Arg	Ile	Tyr	Asp	Phe	Asn	Glu	Asn	Gly	Phe	Ile	Asp	Glu	Glu	
				110					115					120	
Asp	Leu	Gln	Arg	Ile	Ile	Leu	Arg	Leu	Leu	Asn	Ser	Asp	Asp	Met	
				125					130					135	
Ser	Glu	Asp	Leu	Leu	Met	Asp	Leu	Thr	Asn	His	Val	Leu	Ser	Glu	
				140					145					150	
Ser	Asp	Leu	Asp	Asn	Asp	Asn	Met	Leu	Ser	Phe	Ser	Glu	Phe	Glu	
				155					160					165	
His	Ala	Met	Ala	Lys	Ser	Pro	Asp	Phe	Met	Tyr	Ser	Phe	Arg	Ile	
				170					175					180	
Arg	Phe	Trp	Gly	Cys											
				185											

<210> 51

<211> 72

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 4371445CD1

<400> 51

Met	Phe	Thr	Ile	Ile	Phe	Pro	Val	Cys	Lys	Asn	Ser	Met	Pro	Val	
1				5					10					15	
Lys	Lys	Thr	Asp	Thr	Asp	Arg	Ala	Leu	Ser	Leu	Leu	Glu	Glu	Tyr	
				20					25					30	
Cys	Lys	Lys	Leu	Arg	Lys	Pro	Glu	Glu	Gln	Leu	Leu	Lys	Asn	Ala	
				35					40					45	
Val	Lys	Lys	Val	Met	Gly	Ile	Phe	Lys	Ser	Ser	Leu	Phe	Gln	Ala	
				50					55					60	
Leu	Leu	Gly	Met	Tyr	Tyr	Glu	Ser	Tyr	Ser	Ser	Phe				
				65					70						

<210> 52

<211> 434

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 5527925CD1

<400> 52

Met	Ala	Ala	Ala	Ala	Gly	Ser	Cys	Ala	Arg	Val	Ala	Ala	Trp	Gly	
1				5					10					15	
Gly	Lys	Leu	Arg	Arg	Gly	Leu	Ala	Val	Ser	Arg	Gln	Ala	Val	Arg	
				20					25					30	
Ser	Pro	Gly	Pro	Leu	Ala	Ala	Ala	Val	Ala	Gly	Ala	Ala	Leu	Ala	
				35					40					45	
Gly	Ala	Gly	Ala	Ala	Trp	His	His	Ser	Arg	Val	Ser	Val	Ala	Ala	
				50					55					60	
Arg	Asp	Gly	Ser	Phe	Thr	Val	Ser	Ala	Gln	Lys	Asn	Val	Glu	His	
				65					70					75	
Gly	Ile	Ile	Tyr	Ile	Gly	Lys	Pro	Ser	Leu	Arg	Lys	Gln	Arg	Phe	
				80					85					90	
Met	Gln	Phe	Ser	Ser	Leu	Glu	His	Glu	Gly	Glu	Tyr	Tyr	Met	Thr	
				95					100					105	
Pro	Arg	Asp	Phe	Leu	Phe	Ser	Val	Met	Phe	Glu	Gln	Met	Glu	Arg	
				110					115					120	
Lys	Thr	Ser	Val	Lys	Lys	Leu	Thr	Lys	Lys	Asp	Ile	Glu	Asp	Thr	
				125					130					135	
Leu	Ser	Gly	Ile	Gln	Thr	Ala	Gly	Cys	Gly	Ser	Thr	Phe	Phe	Arg	
				140					145					150	
Asp	Leu	Gly	Asp	Lys	Gly	Leu	Ile	Ser	Tyr	Thr	Glu	Tyr	Leu	Phe	
				155					160					165	
Leu	Leu	Thr	Ile	Leu	Thr	Lys	Pro	His	Ser	Gly	Phe	His	Val	Ala	

	170		175		180
Phe Lys Met Leu	Asp Thr Asp Gly Asn	Glu Met Ile Glu Lys	Arg		
	185		190		195
Glu Phe Phe Lys	Leu Gln Lys Ile Ile	Ser Lys Gln Asp Asp	Leu		
	200		205		210
Met Thr Val Lys	Thr Asn Glu Thr Gly	Tyr Gln Glu Ala Ile	Val		
	215		220		225
Lys Glu Pro Glu	Ile Asn Thr Thr Leu	Gln Met Arg Phe Phe	Gly		
	230		235		240
Lys Arg Gly Gln	Arg Lys Leu His Tyr	Lys Glu Phe Arg Arg	Phe		
	245		250		255
Met Glu Asn Leu	Gln Thr Glu Ile Gln	Glu Met Glu Phe Leu	Gln		
	260		265		270
Phe Ser Lys Gly	Leu Ser Phe Met Arg	Lys Glu Asp Phe Ala	Glu		
	275		280		285
Trp Leu Leu Phe	Phe Thr Asn Thr Glu	Asn Lys Asp Ile Tyr	Trp		
	290		295		300
Lys Asn Val Arg	Glu Lys Leu Ser Ala	Gly Glu Ser Ile Ser	Leu		
	305		310		315
Asp Glu Phe Lys	Ser Phe Cys His Phe	Thr Thr His Leu Glu	Asp		
	320		325		330
Phe Ala Ile Ala	Met Gln Met Phe Ser	Leu Ala His Arg Pro	Val		
	335		340		345
Arg Leu Ala Glu	Phe Lys Arg Ala Val	Lys Val Ala Thr Gly	Gln		
	350		355		360
Glu Leu Ser Asn	Asn Ile Leu Asp Thr	Val Phe Lys Ile Phe	Asp		
	365		370		375
Leu Asp Gly Asp	Glu Cys Leu Ser His	Glu Glu Phe Leu Gly	Val		
	380		385		390
Leu Lys Asn Arg	Met His Arg Gly Leu	Trp Val Pro Gln His	Gln		
	395		400		405
Ser Ile Gln Glu	Tyr Trp Lys Cys Val	Lys Lys Glu Ser Ile	Lys		
	410		415		420
Gly Val Lys Glu	Val Trp Lys Gln Ala	Gly Lys Gly Leu Phe			
	425		430		

<210> 53

<211> 1629

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 129042CB1

<400> 53

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gggtggccga	ttactgcgag	aacaactaca	tacagtcagc	agataagcag	agagccctag	180
aagaaaccaa	agcctacacc	acccaatcct	tagcaagtgt	tgcctatctg	ataaacacct	240
tggccaacaa	tgtcctgcag	atgctggata	tccaggcatc	ccagctacga	aggatggaat	300
cttcaatcaa	tcatatttca	caaacagttg	atattcataa	agagaaagtt	gcaagaagag	360
aaattggtat	tttgactacc	aataaaaaa	cttcaaggac	acataagatt	attgctccag	420
ccaaccttga	acgaccagtt	cgttatatta	gaaaacctat	tgactataca	attctagatg	480
atattggaca	tggagtaaag	gtgagtaccc	agaacatgaa	gatgggtggg	ctgccgcgta	540
caacacctcc	aactcagaag	ccccctagtc	cccctatgtc	agggaaaggg	acacttgggc	600
ggcactcccc	ctatcgca	ctggagccag	tgcgtcctcc	agtgggtacca	aatgattacg	660
tacctagccc	aaccgcgtat	atggctccct	cgcagcagag	ccctgtgagg	acagcttctg	720
tgaatcaaag	aaatcgaact	tacagcagca	gtgggagtag	tggagggagc	cacccaagta	780
gtcggagcag	cagtcgagag	aacagtggaa	gtggtagtgt	gggggttctt	attgctgttc	840
ctactccatc	tcctcccagt	gtctttccag	gtcatcctgt	acagttctac	agcatgaata	900
ggcctgcctc	tcgcataact	cccccaacaa	tagggggctc	gttgccctat	agacgccttc	960
cttccattac	ttcacaaaca	agccttcaga	atcagatgaa	tggaggacct	ttttatagcc	1020
agaatccagt	ttcagataca	ccacctccac	cgccacctgt	ggaagaacca	gtctttgatg	1080
agtctccccc	acctctctct	cctccagaag	attacgaaga	ggaggaagct	gctgtgggtg	1140
aggtatgtga	tccttatgtc	gaagaggacc	caccgtgggc	tccacgttct	tacttggaaa	1200
aggttgtggc	aatttatgac	tatacaaaa	acaaggaaga	tgagctgtcc	tttcaggaag	1260
gagccattat	ttatgtcatc	aagaagaatg	acgatgggtg	gtatgaggga	gttatgaatg	1320

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gagtgaactgg gcttttttccct ggggaattacg ttgagttctat catgcattat tctgagtaaa 1380
gctcagcagg gctgtgcttg cctcacagga atagtcagggt ctccccagat tatctgaagg 1440
ccctggggat tccactccag taaagtagaa tgaaggatac aaatgataaa aattacactt 1500
ttttttttgg tttattcccc agtattaaaa acaaagcaag ctgagttctga acaaattggat 1560
ctttctgcca tcatttgtac aatgctgagc tgtctggatt gaaataaaaat gaccattttt 1620
atgtatgtc                                     1629

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<210> 54
 <211> 1257
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 778003CB1

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<400> 54
gcacctgac tttctcatcc ttccctgctc ttcccttctc ctccacctcc tctctctcct 60
tgaggaaagg ggcccgagga agggcatgtg ggggcccctc tgacagtggc cggattgggg 120
tgacaggcgc ccaaattggc aagtggctac gggactacct gagctttggg ggtcggaggc 180
ccccctcgca gccgcccacc cgggactaca ccgagagcga catcctgagg gctaccgcg 240
cgcaagaaga cctggacttt gaggacccct atgaggacgc ggagagccgc ttggagccgg 300
accccgcggg ccctggggac tccaagaacc ccggagatgc caagtatggt tctcccaagc 360
accggctcat caaggtggag gctgcgagata tggccagagc caaggccctt ctgggcgggc 420
ccggggagga gctggaagcc gacactgagt atttagacct ctttgatgct cagcctcatc 480
ctgcaccccc ggatgatggg tacatggagc cctacgatgc ccaatgggtc atgagtgaac 540
ttcccggcag aggggtgcag ctctatgaca cccttatga ggaacaggac ccagagacag 600
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<223> Incyte ID No: 2149037CB1

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<210> 68
 <211> 1156
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 4155412CB1

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<400> 68
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 <211> 1981
 <212> DNA
 <213> Homo sapiens

<220>
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<211> 1832

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 5676581CB1

<400> 70

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<210> 71

<211> 1772
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 034159CB1

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<210> 72
 <211> 1488
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 129023CB1

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 aaaagcctct catgctaacg ttgcagaccc cagagggctc tgtgtgggtg tggagatggc 300
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<210> 73

<211> 2430

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1358940CB1

<400> 73

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<211> 1411

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature
<223> Incyte ID No: 1682320CB1

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<210> 75
<211> 653
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1728263CB1

<400> 75
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cctactatcg tggattttta actttggaag atttcaaaaa agcatttagg cagggtggctc 420
ccaaattacc ggaaggact gttcttgagg tattcagga agtagatcga gattcagatg 480
gtcacgtcag ctttagagac tttgaatag ccctgaacta tggacagaag gaagcctaac 540
tattgtgaac tacttttggg aactctgggg agatcaatag attgtaatgt cagcagactc 600
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<210> 76
<211> 1448
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1867626CB1

<400> 76
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tggtatttac aagagagaaa tcatattacc taagagaact aattgaattg gcagcatcct 180
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acggagaaat tcctttggaa gttattccgt agcataagag ctgaaacttc agagcaagtt 300
ttcatgggac aaaatggggg aacaacctat cttcagcact cgagctcatg tcttccaaat 360

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tagctctg						1448

<210> 77

<211> 1538

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1990126CB1

<400> 77

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cagaaaaaat	aatgaaacaa	actgaagtgt	tattgcagcc	aaatccaaat	gccaggatag	300
aagaatttgt	ttatgagaaa	ctggatagaa	aagctccaag	tcgtataaac	aaccagaaac	360
ttttgggaca	atatatgatt	gatgcaggga	ctgagtttgg	cccaggaaca	gcttatggta	420
atgcccttat	taaatgtgga	gaaacccaaa	aaagaattgg	aacagcagac	agagaactga	480
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catccaatta	tcttagtaac	aacaatcaga	cttctgtgac	acctgtacca	tcagttttac	900
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<210> 78

<211> 998

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2104180CB1

<400> 78

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cagcgcgggc cgggtgtacat cgggtgagctc ccgcaggact tccctccgcat cagcccccaca 240
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<210> 79

<211> 1086

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2122241CB1

<400> 79

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<210> 80

<211> 2323

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2580428CB1

<400> 80

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ccctgctgtc agtgcgcctg cgcgcggggt cggcgccgag gttcttgact cctgtgccg 180
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gcattactgc cttgtcttga tgagtctcgt ttgaaaatc ttggagtaag ttccttggg 480
gagaggaaga agctgcttag ttatatccag cgattgggtc aaatccacgt tgatacaatg 540

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aaggtaatta atgatcctat ccatggccac attgagctcc accctctcct cgtccgaatc 600
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<210> 81
 <211> 669
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 3397189CB1

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<400> 81
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gagaccattc ccaaattgga ggtcatcatt catttaccac gtgtttcctt catgccagc 600
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<210> 82
 <211> 1606
 <212> DNA
 <213> Homo sapiens

<220>
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 <223> Incyte ID No: 4881249CB1

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<400> 82
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gaggtgcagg ggaagtacgt gaagaaggag acgtcgcctc tgcttcggaa tcttatgcct 180

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tcattcatcc	ggcatggtcc	aacaattcca	agacgaactg	atatctgtct	tccagattca	240
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<210> 83

<211> 1980

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 431871CB1

<400> 83

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(54) Title: HUMAN INTRACELLULAR SIGNALING MOLECULES

(57) Abstract: The invention provides human intracellular signaling molecules (INTRA) and polynucleotides which identify and encode INTRA. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of INTRA.